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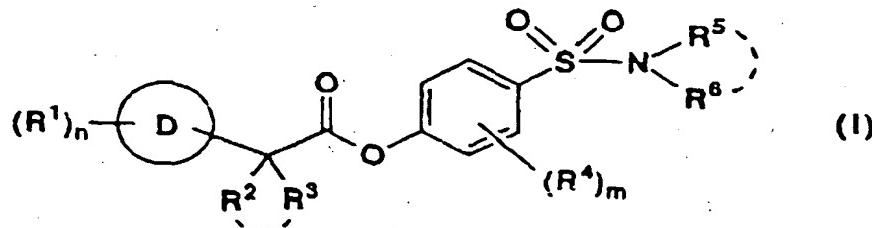
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(54) —Sulfonamide derivatives with elastase inhibiting activity

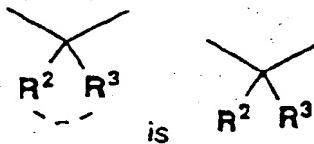
(57) Sulfonamide derivatives of the formula (I)



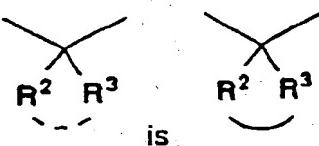
wherein R¹ is, *inter alia*, alkyl, alkoxy, hydroxy, keto, nitro, halogen, trihalomethyl, cyano, amidino and -COOR⁷ (in which R⁷ is hydrogen or alkyl), n is an integer from 0 to 5;



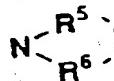
is a carbocyclic ring or heterocyclic ring;



in which R² and R³ each is hydrogen, alkyl, alkoxy, halogen, trihalomethyl or phenyl, or R² and R³, taken together, represent alkylidene, or



in which R² and R³, taken together with the carbon atom to which they are attached represent cycloalkyl; R⁴ is alkyl or alkoxy or two of R⁴, attached to the benzene nucleus at ortho positions relative to each other, taken together, represent alkylene; m is an integer from 0 to 4; and



is optionally substituted amino or a nitrogen-containing ring, are described as new pharmaceutical compounds having inhibitory activity or elastase.

Description

This invention relates to sulfonamide derivatives useful as pharmaceuticals. More particularly, this invention relates to:

- 5 (1) sulfonamide derivatives of formula (I) as hereinafter defined, and non-toxic salts, acid addition salts and solvates thereof,
- (2) processes for their preparation, and
- (3) pharmaceutical compositions containing them as active ingredient.

10 Lysosomal hydrolases of neutrophils have an important role in the defence reaction of organisms against tissue damage caused, for example, by microbes or inflammation.

Elastase and cathepsin G, which are neutral serine proteinases existing locally in azurophil granules, play a part in the decomposition of connective tissue.

15 In particular, elastase degrades elastic connective tissue by cleaving the cross-linking of elastin which directly maintains the elasticity of e.g. lung tissue, by cleaving the hydrophobic part of protein [J. Cell. Biol., 40, 366 (1969)] and selectively degrading the cross-linking of collagen as well as elastin [J. Biochem., 84, 559 (1978)]. It also acts on tissue proteins such as proteoglycans [J. Clin. Invest., 57, 615 (1976)]. It will be seen therefore that elastase plays an important role in the metabolism of connective tissue.

20 Elastase is inactivated by α_1 -proteinase inhibitor (α_1 -PI) which is a common inhibitor for serine proteinases *in vivo* and an imbalance of enzyme and inhibitor causes the destruction of tissue [Schweiz. Med. Wshir., 114, 895 (1984)].

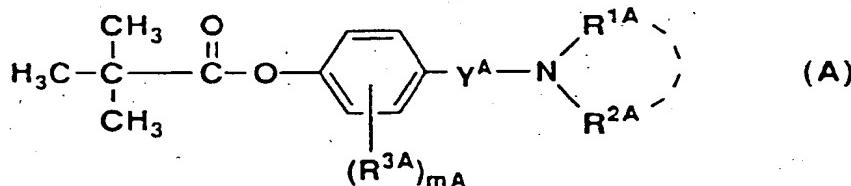
The turnover of elastin in normal tissue is very slow [Endocrinology, 120, 92 (1978)], but pathological acceleration in degradation of elastin is found under various diseased conditions such as pulmonary emphysema [Am. Rev. Respir. Dis., 110, 254 (1974)], atherosclerosis [Lab. Invest., 22, 228 (1970)] and rheumatoid arthritis [in Neutral Proteases of

25 Human Polymorphonuclear Leukocytes, Urban and Schwarzenberg, Baltimore - Munich (1978), page 390], which suggests a relationship between elastase and diseases [Infection Inflammation Immunity, 13, 13 (1983)].

In view of this background, many studies on the development of elastase inhibitors have been conducted recently, and various substances inhibiting elastase have been proposed and many patent applications have been filed.

For example,

- 30 (1) it is disclosed in EP-A-0347168 that the compound of formula (A)



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(wherein Y^A is sulfonyl or carbonyl;

(i) R^{1A} and R^{2A} , which may be the same or different, each represent, inter alia, hydrogen atom, C1-16 alkyl or a group of the formula

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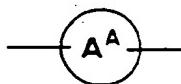


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(wherein X^A is bond, sulfonyl, C1-4 alkylene, C1-4 alkyl substituted by -COOH or benzyloxycarbonyl;

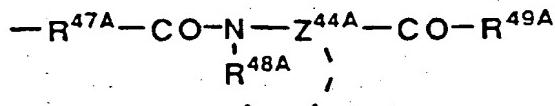
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is carbocyclic ring or heterocyclic ring;
 nA is 1-5; and



R^{4A} which may be the same or different, represent, inter alia, hydrogen atom, C1-8 alkyl, C1-14 alkoxy, C1-6 alkylthio, hydroxy, halogen atom, nitro, trihalomethyl, -Z^{41A}, COOR^{43A}, -CONR^{41A}R^{42A}, a group of the formula

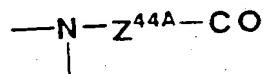
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in which the group of formula

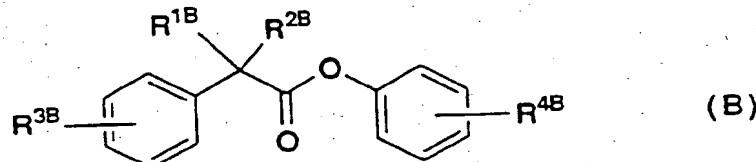
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is an amino acid residue;

- 20 R^{49A} is hydroxy, C1-4 alkoxy, amino, amino or carbamoyl substituted by one or two C1-4 alkyl, etc.) or
(ii) R^{1A} and R^{2A} and the nitrogen atom bonded to R^{1A} and R^{2A} together represent a heterocyclic ring containing at least one nitrogen atom and substituted by -COOH or an unsubstituted heterocyclic ring containing at least one nitrogen atom;
25 R^{3A} is hydrogen atom, hydroxy, C1-6 alkyl, etc.; and
mA is 1-4)
- and non-toxic salts and acid addition salts thereof have an inhibitory activity on elastase;
- (2) it is disclosed in EP-A-0465802 that the compound of formula (B)

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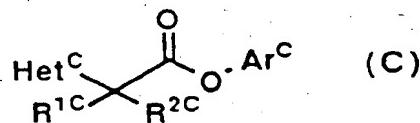
35

(wherein R^{1B} and R^{2B}, which may be the same or different, each represent, hydrogen, C1-6 alkyl or C3-6 cycloalkyl, or R^{1B} and R^{2B} taken together represent -(CH₂)_{nB}- (in which nB is 1-6);

- 40 R^{3B} is one to five of hydrogen, halogen, C1-12 haloalkyl, C1-12 alkyl, C1-12 alkoxy, C2-12 alkenyl, C3-12 cycloalkyl, mono or bicyclic aryl, -Z^BR^{5B} (in which Z^B is O, S, S(O) or SO₂; R^{5B} is hydrogen, C1-18 alkyl, C3-12 cycloalkyl, or phenyl), -NR^{6B}R^{7B} (in which R^{6B} and R^{7B}, which may be the same or different, each represent hydrogen, C1-12 alkyl, C3-6 cycloalkyl, phenyl, C1-12 alkoxy or -C(O)-R^{3B}, or R^{6B} and R^{7B} taken together represent -C(O)CH₂CH₂-C(O)-, -C(O)-C₆H₄-C(O)- or -(CH₂)_{XB}- (XB is 2, 3, 4, 5 or 6), or morpholino, imizazolyl or piperazino, etc., bonded to phenyl ring on nitro atom; and
- 45 R^{4B} is one to five of hydrogen, halogen, nitro, -C(O)CH₃, S(O)_{pB}R^{9B} (pB is 0, 1 or 2; R^{9B} is hydroxy, -ONa, C1-12 alkyl optionally substituted, cycloalkyl optionally substituted))
- and non-toxic pharmaceutically acceptable salts thereof have an inhibitory activity on elastase;

(3) it is disclosed in EP-A-0484949 that the compound of formula (C)

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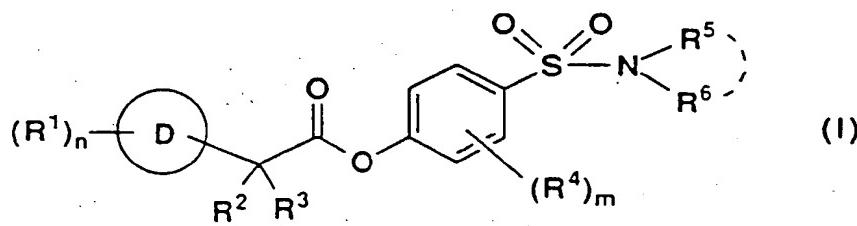
(wherein R^{1C} and R^{2C}, which may be the same or different, each represent hydrogen, C1-6 alkyl or C3-6 cycloalkyl, or R^{1C} and R^{2C} taken together represent -(CH₂)_{nC}- (in which nC is 1-6);

Ar^{C} is optionally substituted phenyl; and
 Het^{C} is heterocyclic ring containing at least one nitrogen atom, sulfur atom or oxygen atom)
have an inhibitory activity on elastase.

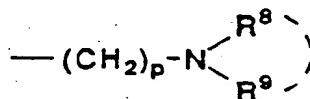
Few of the compounds known to have an inhibitory activity on elastase have been reported to show an inhibitory activity on elastase by oral administration. Most compounds could not be expected to show an effect by oral administration. In order to show activity by oral administration, pharmaceutical agents must be readily absorbed by the digestive organs and must maintain their activity until they are transported to an active site. Therefore, only those compounds having good stability, absorbability and/or solubility in the digestive organs are expected to show sufficient activity by oral administration.

Energetic investigations have been carried out to find new compounds having good inhibitory activity on elastase and also having high safety. As a result, the present inventors have found that these aims may be accomplished by sulfonamide derivatives of the formula (I). Further, we have found that the new compounds have good stability, absorbability and solubility and are active as elastase inhibitors by oral administration.

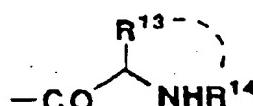
The present invention provides a sulfonamide derivative of formula (I):



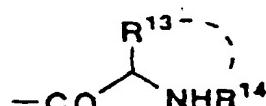
wherein R¹ is C₁-8 alkyl, C₁-8 alkoxy, hydroxy, keto, nitro, halogen atom, trihalomethyl, cyano, amidino, -COOR⁷ (in which R⁷ is hydrogen atom or C₁-8 alkyl), or



(in which p is an integer from 0 to 4, and R⁸ and R⁹ each, independently, is hydrogen atom, C₁-4 alkyl, C₂-5 acyl, -COOR¹⁰ (in which R¹⁰ is hydrogen atom or C₁-8 alkyl), -CONR¹¹R¹² (in which R¹¹ and R¹² each, independently, is hydrogen atom or C₁-4 alkyl),



(in which



is an α -amino acid residue), or R⁸ and R⁹ taken together with the nitrogen atom to which they are attached represent an aliphatic heterocyclic ring which is unsubstituted or substituted by C₁-4 alkyl or phenyl C₁-4 alkyl);

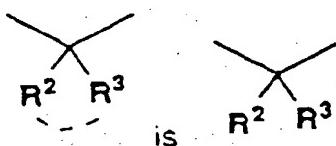
n is an integer from 0 to 5;

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is a carbocyclic ring or heterocyclic ring;

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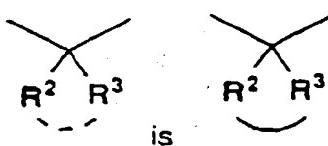


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in which R² and R³ each, independently, is hydrogen atom, C1-4 alkyl, C1-4 alkoxy, halogen atom, trihalomethyl or phenyl, or

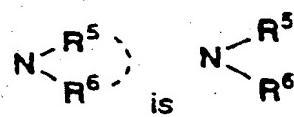
20 R² and R³, taken together, represent C1-4 alkylidene, or

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in which R² and R³, taken together with the carbon atom to which they are attached represent C3-7 cycloalkyl;
30 R⁴ is C1-4 alkyl or C1-4 alkoxy or two of R⁴, attached to the benzene nucleus at ortho positions relative to each other, taken together, represent C3-5 alkylene;
m is an integer from 0 to 4; and

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40 in which R⁵ and R⁶ each, independently, is

- 1) hydrogen atom,
- 2) hydroxy,
- 3) C1-8 alkyl,
- 4) C1-8 alkoxy

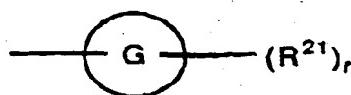
45 5) phenyl C1-4 alkoxy,
6) amidino,
7) -M-R¹⁶

(in which M is single bond or C1-8 alkylene), and

R¹⁶ is

50 i) -NR¹⁷R¹⁸ (in which R¹⁷ and R¹⁸ each, independently, is hydrogen atom or C1-4 alkyl),
ii) -CONR¹⁹R²⁰ (in which R¹⁹ and R²⁰ each, independently, is hydrogen atom or C1-4 alkyl),
iii)

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(in which

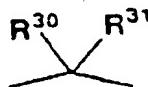


is a carbocyclic ring,

10 r is an integer from 0 to 5, and

R²¹ is C1-4 alkyl, C1-4 alkoxy, nitro, amidino, -COOR²² (in which R²² is hydrogen atom, C1-8 alkyl, phenyl or phenyl C1-4 alkyl), -SO₃H, -CONR²³-E-R²⁴ (in which R²³ is hydrogen atom or C1-4 alkyl, E is 1-4 alkylene and R²⁴ is -COOR²⁵ (in which R²⁵ is hydrogen atom, C1-8 alkyl, phenyl or phenyl C1-4 alkyl) or tetrazole ring), tetrazole ring or morpholino ring).15 iv) heterocyclic ring, unsubstituted or substituted by 1 to 4 substituents selected from C1-4 alkyl, C1-4 alkoxy, hydroxy, phenyl C1-4 alkyl, -COOR²⁶ (in which R²⁶ is hydrogen atom, C1-8 alkyl, phenyl or phenyl C1-4 alkyl), hydroxy C1-4 alkyl or C2-4 alkoxyalkyl),5) C1-8 alkyl substituted by one or two of -OR²⁷ (in which R²⁷ is hydrogen atom, C1-4 alkyl, C2-4 alkoxyalkyl or C2-4 alkyl substituted by -OR²⁸ (in which R²⁸ is hydrogen atom or C2-4 alkoxyalkyl)),20 9) -J-COOR²⁹ (in which R²⁹ is hydrogen atom, C1-8 alkyl, phenyl or phenyl C1-4 alkyl, and J is a single bond, -(CH₂)_s - or

25



(in which s is an integer from 2 to 6, and

30 R³⁰ and R³¹ each, independently, is

i) hydrogen atom.

ii) C1-8 alkyl.

iii) -COOR³² (in which R³² is hydrogen atom, C1-8 alkyl, phenyl or phenyl C1-4 alkyl).

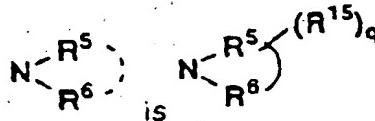
iv) carbocyclic or heterocyclic ring, unsubstituted or substituted by one or more substituents selected from C1-4 alkyl,

35 C1-4 alkoxyalkyl, amino, nitro, hydroxy, halogen atom, nitrile, guanidino and amidino, or

v) C1-8 alkyl substituted by one or more substituents selected from hydroxy, -COOR³³ (in which R³³ is hydrogen atom, C1-8 alkyl, phenyl or phenyl C1-4 alkyl), -NR³⁴R³⁵ (in which R³⁴ and R³⁵ each, independently, is hydrogen atom or C1-4 alkyl), carbocyclic or heterocyclic ring, unsubstituted or substituted by one or more substituents selected from

40 C1-4 alkyl, C1-4 alkoxyalkyl, amino, nitro, hydroxy, halogen atom, nitrile, guanidino and amidino, with the proviso that a carbon atom of C1-8 alkyl may be replaced by a sulfur atom), or

45

in which R⁵ and R⁶, taken together with the nitrogen atom to which they are attached represent a heterocyclic ring, q is an integer from 0 to 4, and50 R¹⁵ is

1) hydroxy;

2) keto,

3) protected keto,

4) C1-4 alkyl,

55 5) C1-4 alkoxy,

6) phenyl,

7) phenoxy,

8) phenyl C1-4 alkyl.

- 9) phenyl C1-4 alkoxy,
 10) nitro,
 11)-COOR³⁶ (in which R³⁶ is hydrogen atom, C1-8 alkyl, C1-4 alkyl substituted by -CONR³⁷R³⁸ (in which R³⁷ and R³⁸ each, independently, is hydrogen atom or C1-4 alkyl), C1-4 alkyl substituted by -NR³⁹R⁴⁰ (in which R³⁹ and R⁴⁰ each, independently, is hydrogen atom or C1-4 alkyl), C1-4 alkyl substituted by -OR⁴¹ (in which R⁴¹ is C2-4 alkyl substituted by -OR⁴² (in which R⁴² is hydrogen atom or C2-4 alkoxyalkyl)) or C1-4 alkyl substituted by piperazino ring),
 12) -NR⁴³R⁴⁴ (in which R⁴³ and R⁴⁴ each, independently, is hydrogen atom, C1-4 alkyl or C2-5 acyl),
 13) -CONR⁴⁵R⁴⁶ (in which R⁴⁵ and R⁴⁶ each, independently, is hydrogen atom, hydroxy, C1-4 alkyl, phenyl C1-4 alkoxy or C1-4 alkyl substituted by hydroxy or -COOR⁴⁷ (in which R⁴⁷ is hydrogen atom or C1-8 alkyl)),
 14) C1-4 alkyl substituted by one or more substituents selected from hydroxy, -COOR⁴⁸ (in which R⁴⁸ is hydrogen atom or C1-8 alkyl), -NR⁴⁹R⁵⁰ (in which R⁴⁸ and R⁵⁰ each, independently, is hydrogen atom or C1-4 alkyl), -OSO₃H or 5- or 6-membered heterocyclic ring containing one or two nitrogen atoms,
 15) 5- or 6-membered heterocyclic ring containing one or two nitrogen atoms,
 16) halogen atom,
 17) -CHO, or
 18) -NR⁵¹-COOR⁵² (in which R⁵¹ and R⁵² each, independently, is hydrogen atom or C1-8 alkyl);
 or a non-toxic salt, acid addition salt or solvate thereof.

The sulfonamide derivatives of the present invention are novel compared with compounds disclosed in the prior art.

To summarize, the compounds of formula (A) described in EP-A-0347168 necessarily contain a pivaloyloxy group.

In contrast, the compounds of the present invention have a ring D which may be substituted by various substituents R¹.

Thus the compounds of the present invention have a chemical structure quite different from that of the compounds of formula (A).

The compounds of formula (B) described in EP-A-0465802 include compounds in which R^{4B} represents S(O)_{pB}R^{9B}. R^{9B} can represent hydroxy, -ONa, optionally substituted C1-12 alkyl or optionally substituted cycloalkyl, but can not represent amino group. Further, the compounds of formula (C) described in EP-A-0484949 include those in which a substituent of Ar^C represents S(O)_{pC}R^{9C}. R^{9C} can represent hydroxy, -ONa, optionally substituted C1-12 alkyl or optionally substituted cycloalkyl, but can not represent amino group.

In contrast, the compounds of the present invention have a sulfonamide group which may be substituted by various substituents. Thus the compounds of the present invention have a chemical structure quite different from that of the compounds of formula (B) and (C).

Furthermore, related compounds show no activity by oral administration, but some compounds in the present invention have good stability, absorbability and solubility, and are, therefore, active as elastase inhibitors by oral administration.

In the formula (I), C1-4 alkyl represented by R², R³, R⁴, R⁸, R⁹, R¹¹, R¹², R¹⁵, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²³, R²⁷, R³⁴, R³⁵, R³⁶, R³⁷, R³⁸, R³⁹, R⁴⁰, R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁹, R⁵⁰, and substituents of aliphatic heterocyclic ring, carbocyclic ring or heterocyclic ring means methyl, ethyl, propyl, butyl and isomers thereof.

In the formula (I), C1-8 alkyl represented by R¹, R⁵, R⁶, R⁷, R¹⁰, R²², R²⁵, R²⁶, R²⁹, R³⁰, R³¹, R³², R³³, R³⁶, R⁴⁷, R⁴⁸, R⁵¹ and R⁵² means methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and isomers thereof.

In the formula (I), C2-4 alkyl represented by R²⁷ and R⁴¹ means ethyl, propyl, butyl and isomers thereof.

In the formula (I), C3-5 alkylene represented by two of R⁴ attached at ortho positions relative to each other means trimethylene, tetramethylene, pentamethylene, and isomers thereof.

In the formula (I), C1-8 alkylene represented by M means methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene and isomers thereof.

In the formula (I), C1-4 alkylene represented by E means methylene, ethylene, trimethylene, tetramethylene and isomers thereof.

In the formula (I), phenyl C1-4 alkyl or phenyl C1-4 alkoxy means C1-4 alkyl or C1-4 alkoxy substituted by a phenyl group.

In the formula (I), phenyl C1-4 alkyl represented by R²⁹, R³², R³³, R¹⁵ and substituents of aliphatic heterocyclic ring or heterocyclic ring means methyl, ethyl, propyl, butyl and isomers thereof, which are substituted by a phenyl group.

In the formula (I), phenyl C1-4 alkoxy represented by R⁵, R⁶, R¹⁵, R⁴⁵ and R⁴⁶ means methoxy, ethoxy, propoxy, butoxy and isomers thereof, which are substituted by a phenyl group.

In the formula (I), C2-5 acyl represented by R⁸, R⁹, R⁴³ and R⁴⁴ means acetyl, propionyl, butyryl, valeryl and isomers thereof.

In the formula (I), C2-4 alkoxyalkyl represented by R²⁷, R²⁸, R⁴² and substituent of heterocyclic ring means methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, methoxypropyl and isomers thereof.

In the formula (I), C1-8 alkoxy represented by R¹, R⁵ and R⁶ means methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy and isomers thereof.

In the formula (I), C1-4 alkoxy represented by R², R³, R⁴, R¹⁵, R²¹ and substituents of carbocyclic ring or hetero-

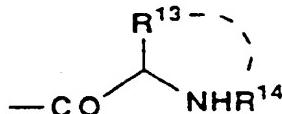
cyclic ring means methoxy, ethoxy, propoxy, butoxy and isomers thereof.

In the formula (I), halogen atom represented by R¹, R², R³ and R¹⁵ means fluorine, chlorine, bromine and iodine.

In the formula (I), the α -amino acid residue represented by

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may be any α -amino acid residue. For example, it may be a residue of glycine, alanine, serine, threonine, cystine, valine, methionine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, aspartic acid, glutamic acid, arginine, glutamine, lysine, histidine or proline.

15 In the formula (I), C3-7 cycloalkyl represented by R² and R³, taken together with the carbon atom to which they are attached means cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

In the formula (I), C1-4 alkylidene represented by R² and R³, taken together, means methylidene, ethylidene, propylidene, butylidene and isomers thereof.

20 In the formula (I), aliphatic heterocyclic ring represented by R⁸ and R⁹, taken together with the nitrogen atom to which they are attached preferably means 5-15 membered mono- or bi-cyclic saturated heterocyclic ring or partly saturated heterocyclic ring containing one or two nitrogen atoms or one nitrogen atom and one sulfur atom or oxygen atom. Examples include pyrroline, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, piperazine, tetrahydropyrimidine, hexahydropyrimidine, tetrahydropyridazine, hexahydropyridazine, hexahydroazepine, dihydrooxazole, tetrahydrooxazole, dihydroisooxazole, tetrahydroisooxazole, dihydrothiazole, tetrahydrothiazole, dihydroisothiazole, tetrahydroisothiazole, morpholine, thiomorpholine, indoline, isoindoline, dihydroindazole, perhydroindazole, dihydroquinoline, tetrahydroquinoline, perhydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydroisoquinoline, dihydropthalazine, tetrahydropthalazine, perhydropthalazine, dihydronaphthyridine, tetrahydro-naphthyridine, perhydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, perhydroquinoxaline, dihydroquinoxaline, tetrahydroquinazoline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline, perhydrocinnoline, dihydrobenzoxazole, perhydrobenzoxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzoimidazole and perhydrobenzoimidazole rings.

30 In the formula (I), carbocyclic ring represented by

35



40 R³⁰ and R³¹ preferably means 3-15 membered mono- or poly-cyclic aromatic hydrocarbon ring or aliphatic hydrocarbon ring. Examples include cyclopentadiene, benzene, pentalene, indene, naphthalene, azulene, cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexene, cyclohexadiene, cycloheptane, dihydroindene, perhydroindene, dihydronaphthalene, tetrahydronaphthalene, perhydronaphthalene, bicyclo[2.2.1]heptane, bicyclo[3.2.2]nonane and adamantine rings.

45 When the above carbocyclic ring has two equivalents, bond sites exist on the same carbon atom or different carbon atom, i.e. when the ring contains two free valencies, two substituents may be attached to the same carbon atom or to different carbon atoms.

In the formula (I), heterocyclic ring represented by

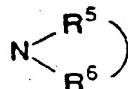
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55 R¹⁶, R³⁰ and R³¹ preferably means 5-15 membered mono- or bi-cyclic aromatic heterocyclic ring, saturated heterocyclic ring or partly saturated heterocyclic ring containing one to four nitrogen atoms, one or two sulfur atoms, one or two oxygen atoms or one nitrogen atom and one sulfur atom or oxygen atom. Examples include pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, furan, pyran, oxepine, thiophene, thiazone (thiopyran), thiopine, oxazole, isooxazole, thiazole, isothiazole, oxazine, oxazepine, thiazine, thiazepine, indole, isoindole, benzo-

furan, isobenzofuran, benzothiophene, isobenzothiophene, indazole, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzoxazole, benzothiazole, benzoimidazole, pyrrolidine, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, piperazine, tetrahydropyrimidine, hexahydropyrimidine, tetrahydropyridazine, hexahydropyridazine, hexahydroazepine, hexahydrodiazepine, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrothiophene, tetrahydrothiophene, dihydrothiazine (dihydrothiopyran), tetrahydrothiazine (tetrahydrothiopyran), dihydrooxazole, tetrahydrooxazole, dihydroisooxazole, tetrahydroisooxazole, dihydrothiazole, tetrahydrothiazole, dihydroisothiazole, tetrahydroisothiazole, morpholine, thiomorpholine, indoline, isoindoline, dihydrobenzofuran, perhydrobenzofuran, dihydroisobenzofuran, perhydroisobenzofuran, dihydrobenzothiophene, perhydrobenzothiophene, dihydroisobenzothiophene, perhydroisobenzothiophene, dihydroindazole, perhydroindazole, dihydroquinoline, tetrahydroquinoline, perhydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydropthalazine, tetrahydropthalazine, perhydrophthalazine, dihydronaphthyridine, tetrahydronaphthyridine, perhydronaphthyridine, dihydroquinazoline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline, perhydrocinnoline, dihydrobenzoxazole, perhydrobenzoxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzoimidazole, perhydrobenzoimidazole, dihydrobenzoxazine, 1,3-dioxaindane, 1,4-benzodioxane, quinuclidine, triazole and tetrazole rings.

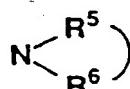
In the formula (I), heterocyclic ring represented by



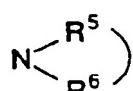
that is, R⁵ and R⁶, taken together with the nitrogen atom to which they are attached, preferably means 3-15 membered mono- or bi-cyclic aromatic heterocyclic ring, saturated heterocyclic ring or partly saturated heterocyclic ring containing one or two nitrogen atoms or one nitrogen atom and one sulfur atom or oxygen atom. Examples include pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, aziridine, azetidine, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, piperazine, tetrahydropyrimidine, hexahydropyrimidine, tetrahydropyridazine, hexahydropyridazine, hexahydroazepine, hexahydrodiazepine, oxazole, isooxazole, thiazole, isothiazole, oxazine, oxazepine, thiazine, thiazepine, indole, isoindole, indazole, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzoxazole, benzothiazole, benzoimidazole, dihydrooxazole, tetrahydrooxazole, dihydroisooxazole, tetrahydroisooxazole, dihydrothiazole, tetrahydrothiazole, dihydroisothiazole, tetrahydroisothiazole, morpholine, thiomorpholine, indoline, isoindoline, perhydroindazole, dihydroquinaline, tetrahydroquinaline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline, dihydrobenzoxazole, perhydrobenzoxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzoimidazole, perhydrobenzoimidazole, 7-azabicyclo[3.2.1]octane, and 3-azabicyclo[3.2.2]nonane rings.

In the formula (I), 5- or 6-membered heterocyclic ring containing one or two nitrogen atoms represented by R¹⁵ means, for example, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, pyrrolidine, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, piperazine, tetrahydropyrimidine or tetrahydropyridazine.

In the formula (I), examples of the ring represented by



to which a protected keto group is bonded, include 1,3-dioxolane and spiro ring derivatives of



One or two keto groups (=O) may be attached to the same or different sulfur atoms as substituents R¹⁵. One group is treated as one R¹⁵.

In formula (I):-

m preferably represents 0, 1 or 2, more preferably 0 or 1.

5 R⁴ preferably represents alkyl or alkoxy of 1-4 carbon atoms, for example methyl, ethyl, isopropyl, methoxy, ethoxy or isopropoxy. Methyl is especially preferred. When one or two substituents R⁴ are present they preferably occupy one or both positions adjacent to the oxygen atom attached to the phenyl ring; compounds in which two substituents are present on the positions ortho and meta to the oxygen attached to the phenyl ring also constitute a feature of the invention; two such substituents may together form a five membered ring fused to the phenyl ring.

10 Compound in which m is 1 and R⁴ represents methyl in the ortho position relative to the oxygen atom attached to the phenyl ring are especially preferred.

15 One of R² and R³ preferably represents hydrogen, methyl, ethyl, or methoxy and the other represents methyl, ethyl, isopropyl, phenyl or trifluoromethyl or R² and R³ together with the carbon atom to they are attached represent ethyldene or cycloalkyl of 3-6 carbon atoms. The ethyl group represented by one of R² and R³ is preferably in β-configuration.

20 D preferably represents phenyl, naphthyl (preferably 1-or 2-naphthyl), thiophenyl (preferably thiophen-2-yl), cyclohexyl, pyridinyl, (preferably pyridin-3-yl), thiazolyl (preferably thiazol-4-yl) imidazolinyl (preferably imidazolin-2-yl), benzimidazolyl (preferably benzimidazol 5-yl), 2H-1,4-benzoxazin-3-on-6-yl, or 1,3-benzodioxol-5-yl, or 1H-1-methyl-2-pyridon-3-yl. Phenyl is especially preferred.

25 n preferably represents 0,1,2 or 3, preferably 0 or 1. R¹ preferably represents alkyl of 1-4 carbon atoms e.g. methyl; alkoxy of 1-4 carbon atoms, e.g. methoxy; amino; amino substituted by two alkyl groups each of 1-4 carbon atoms, for example dimethylamino; methyl substituted by carbamoyl; methyl substituted by alkanoyl of 2-5 carbon atoms for example by acetyl; nitro; hydroxy; cyano; carboxy, trihalomethyl, e.g. trifluoromethyl; amidino; amino substituted by alkoxy carbonyl; halogen, e.g. chlorine; pyrrolidinyl; piperidinyl; perhydroazepinyl; or morpholinyl or piperazinyl optionally substituted on the 4-position by benzyl.

30 Compounds in which D represents mono substituted phenyl constitute a feature of the invention: when D is substituted phenyl at least one substituent is preferably on the 4-position. Preferred 4-substituted phenyl groups are those in which the substituent is a 5-, 6- or 7-membered nitrogen-containing ring attached to phenyl via the nitrogen atom: pyrrolidin-1-yl is preferred.

35 In the grouping NR⁵R⁶, when R⁵ and R⁶, taken together with the nitrogen atom to which they are attached do not represent a heterocyclic ring, the grouping NR⁵R⁶ preferably represents hydrogen; methyl; ethyl; propyl; methoxy; benzyl; methoxymethoxyethyl; 1-hydroxyethyl; hydrogen is especially preferred, and the other represents phenyl; phenyl substituted substituents, e.g. 2-((1-carboxymethyl)aminocarbonyl)phenyl, 4-nitrophenyl; heterocyclic ring, e.g. quinuclidine, piperidine, pyridine, imidazole, morpholine, tetrazole; C1-8 alkyl substituted by heterocyclic ring, e.g. piperazin-1-ylethyl, piperadim-1-ylethyl, morpholin-1-ylethyl, pyridin-2-ylethyl, pyrrol-2-ylethyl; morpholin-1-ylethyl is especially preferred.

40 In the grouping NR⁵R⁶, when R⁵ and R⁶, taken together with the nitrogen atom to which they are attached represent a heterocyclic ring, the ring preferably represents pyrrolidine; indole; indoline; perhydroindole; benzoimidazole; morpholine; piperidine; piperazine; 7-azabicyclo[3.2.1]octane, 3-azabicyclo[3.2.2]nonane; tetrahydrooxazole; tetrahydrothiazole; imidazole; hexahydrodiazepine; aziridine; azetidine; piperazine is especially preferred.

45 In the grouping NR⁵R⁶, when R⁵ and R⁶, taken together with the nitrogen atom to which they are attached represent a heterocyclic ring, R¹⁵ preferably represents hydroxy; C1-4 alkyl substituted by a hydroxy, e.g. hydroxymethyl; C1-4 alkyl substituted by a heterocyclic ring, e.g. pyrrolidin-1-ylmethyl; benzyloxy; amino; methoxy; dimethylamino; acetylamino; methyl, nitro; halogen, e.g. fluorine; keto; carboxy; ester, e.g. ethoxycarbonyl, t-butoxycarbonyl, 2-aminoethoxycarbonyl, 2-(2-hydroxyethoxy)ethoxycarbonyl, 2-(piperazin-1-yl)ethoxycarbonyl; amide, e.g. carboxymethylaminocarbonyl; carboxy is especially preferred.

50 In the grouping NR⁵R⁶, when R⁵ and R⁶, taken together with the nitrogen atom to which they are attached represent a heterocyclic ring, q preferably represents 0, 1 or 2, more preferably 0 or 1.

Throughout the specification including claims, it may be easily understood by those skilled in the art, that all isomers are included in the present invention. For example, the alkyl, alkylene and alkenylene groups include straight-chain and also branched-chain ones. Double bond in alkenylene includes E, Z and EZ mixture. Accordingly, all isomers produced by the existence of asymmetric carbon atoms are included in the present invention when groups such as branched-chain alkyl are present.

55 The compounds of the formula (I), of the present invention may be converted into the corresponding non-toxic salts or acid addition salts by methods known *per se*.

Water-soluble salts are preferred. Suitable salts, for example, include salts of alkali metals (e.g. potassium or sodium), salts of alkaline earth metals (e.g. calcium or magnesium), ammonium salts, salts of pharmaceutically-acceptable organic amines (e.g. tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine,

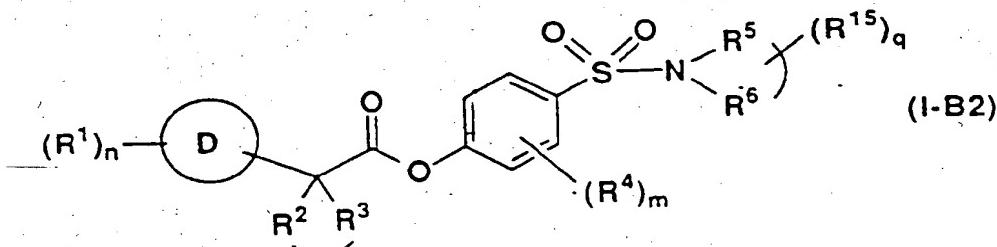
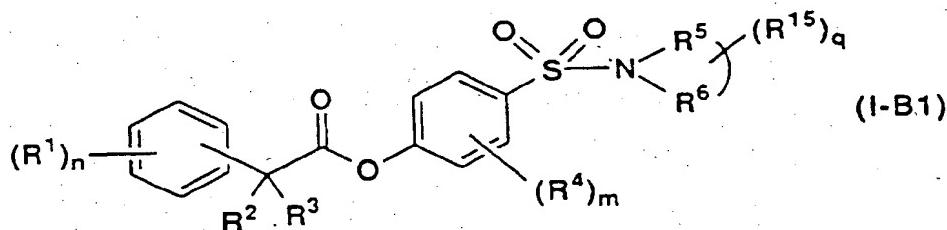
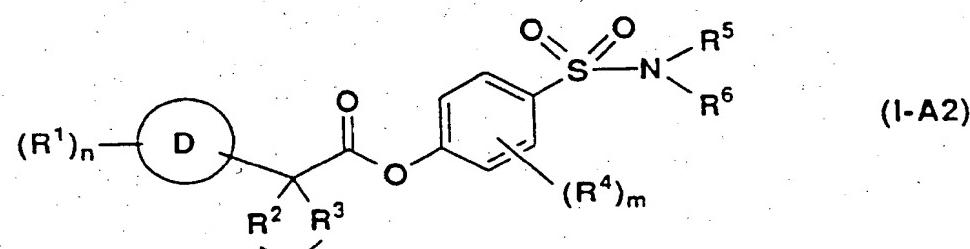
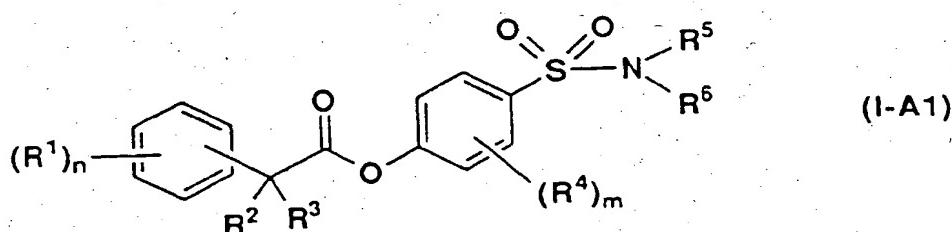
benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)amine, lysine, arginine or N-methyl-D-glucamine).

Water-soluble acid addition salts are also preferred. Suitable acid addition salts, for example, include the salts with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and nitric acid, and the salts with organic acids such as acetic acid, trifluoroacetic acid, lactic acid, tartaric acid, oxalic acid, fumaric acid, maleic acid, benzenesulfonic acid, toluenesulfonic acid, isethionic acid, glucuronic acid and gluconic acid.

The compounds of the formula (I) or salts, of the present invention may be converted into the corresponding solvates by methods known *per se*.

Water-soluble solvates are preferred. Suitable solvates, for example, include the salts with water or with alcohol solvents such as ethanol.

Preferred compounds of the present invention are of the following formulae (I-A1), (I-A2), (I-B1) and (I-B2).

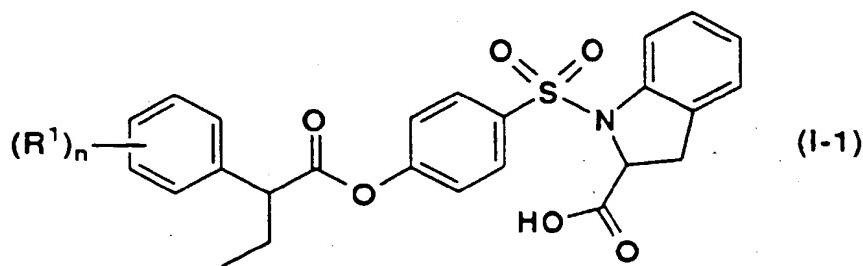


(wherein all symbols are as hereinbefore defined).

55 Representative compounds of the present invention are illustrated by the compounds in the following Tables 1-46 and the non-toxic salts and acid addition salts thereof.

In the Tables, Me is methyl, Et is ethyl, Pr is propyl, iPr is isopropyl and tBu is tert-butyl.

Table 1



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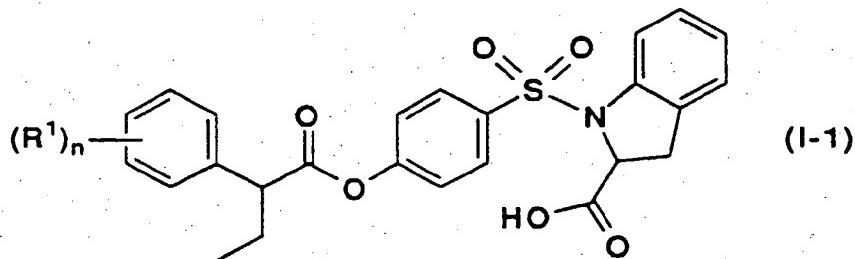
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No.	$(R^1)_n - \text{C}_6\text{H}_4 - \text{CH}_2 -$	No.	$(R^1)_n - \text{C}_6\text{H}_4 - \text{CH}_2 -$
1		6	
2		7	
3		8	
4		9	
5		10	

Table 1(continued)



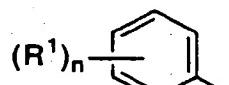
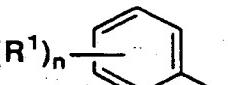
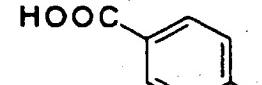
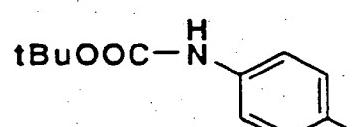
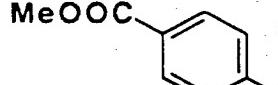
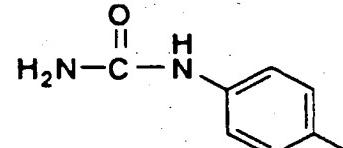
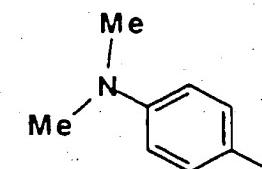
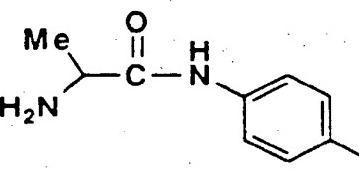
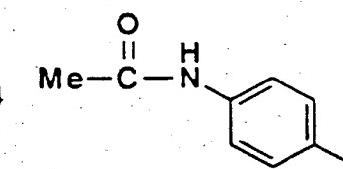
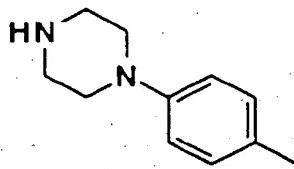
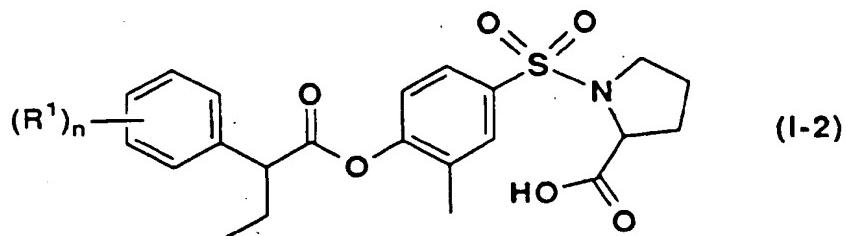
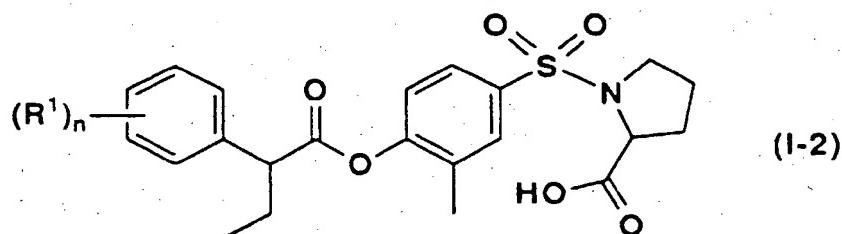
No.	$(R^1)_n$ - 	No.	$(R^1)_n$ - 
11		15	
12		16	
13		17	
14		18	

Table 2



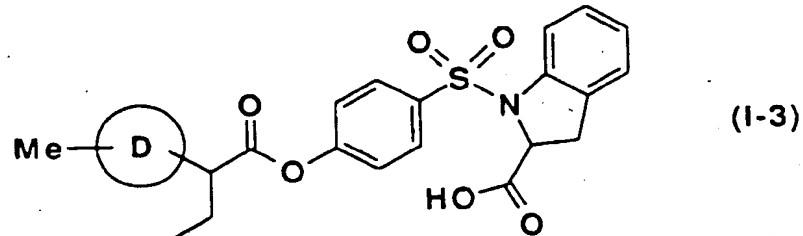
No.	$(R^1)_n-$	No.	$(R^1)_n-$
1		6	
2		7	
3		8	
4		9	
5		10	

Table 2 (continued)



No.	$(R^1)_n-$	No.	$(R^1)_n-$
11		15	
12		16	
13		17	
14		18	

Table 3



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No.	Me-D	No.	Me-D
1		6	
2		7	
3		8	
4		9	
5		10	

Table 4

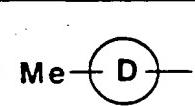
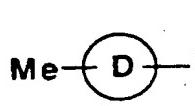
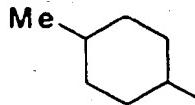
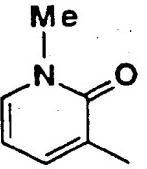
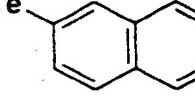
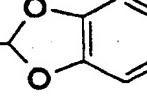
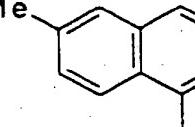
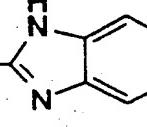
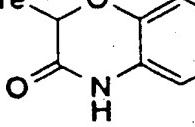
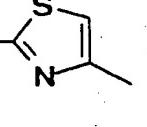
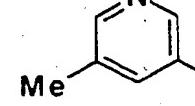
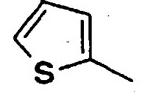
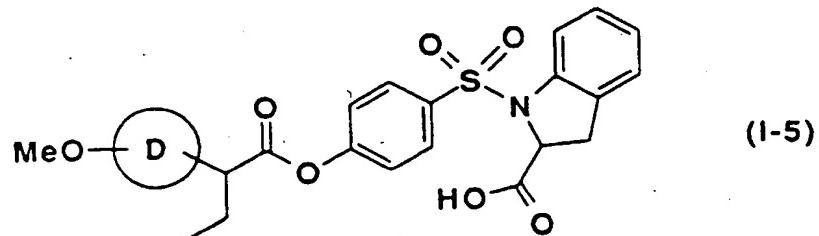
No.		No.	
1		6	
2		7	
3		8	
4		9	
5		10	

Table 5



No.	MeO—D—	No.	MeO—D—
1		6	
2		7	
3		8	
4		9	
5		10	

Table 6

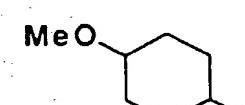
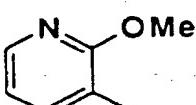
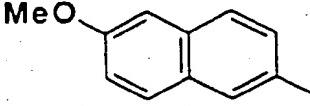
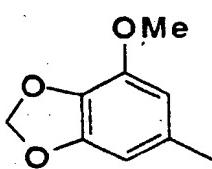
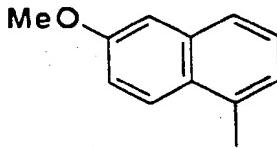
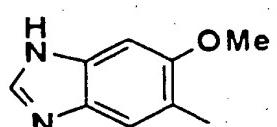
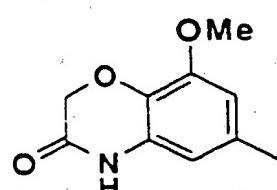
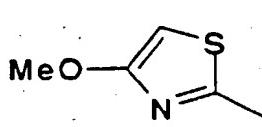
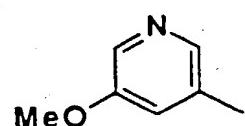
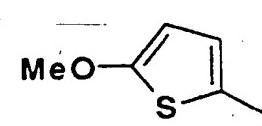
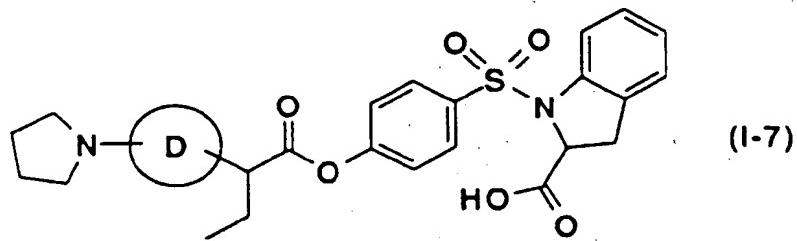
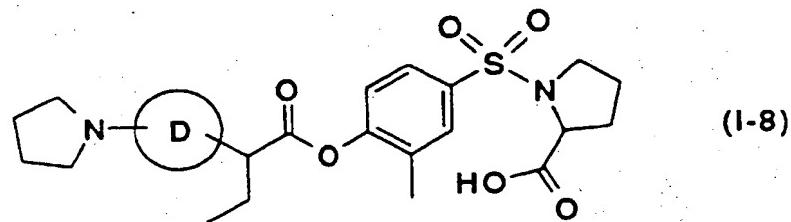
No.	$\text{MeO}-\text{D}$	No.	$\text{MeO}-\text{D}$
1		6	
2		7	
3		8	
4		9	
5		10	

Table 7

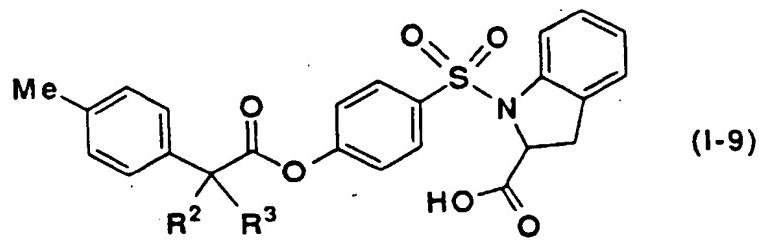


No.		No.	
1		6	
2		7	
3		8	
4		9	
5		10	

Table 8

No.		No.	
1		6	
2		7	
3		8	
4		9	
5		10	

Table 9



15

No.	$\text{R}^2 \text{ } \text{R}^3$	No.	$\text{R}^2 \text{ } \text{R}^3$
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

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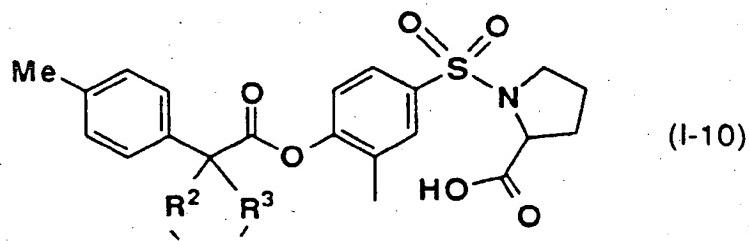
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Table 10



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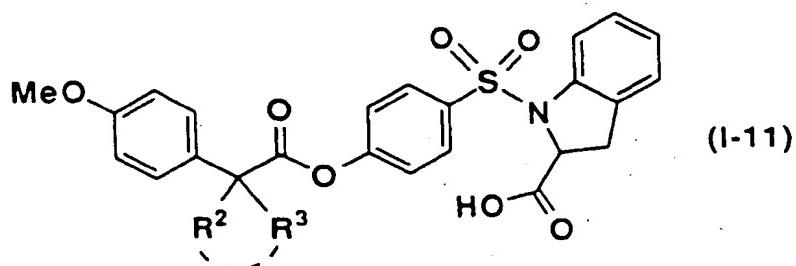
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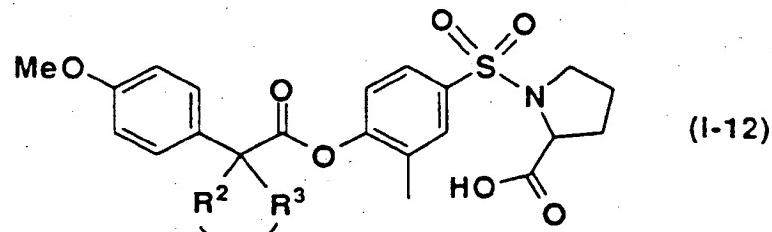
No.	R^2 R^3	No.	R^2 R^3
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 11



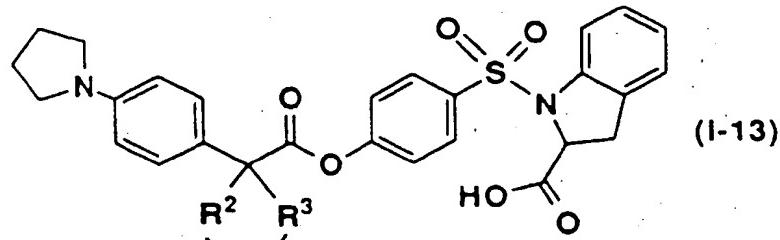
No.	$\text{R}^2 \text{---} \text{R}^3$	No.	$\text{R}^2 \text{---} \text{R}^3$
1	H --- H	8	Cyclopropane
2	Me --- H	9	Cyclobutane
3	Me --- Me	10	Cyclopentane
4	Et --- Et	11	Cyclohexane
5	MeO --- H	12	Chloromethyl
6	Pr --- H	13	Trifluoromethyl
7	iPr --- H	14	Phenylmethyl

Table 12



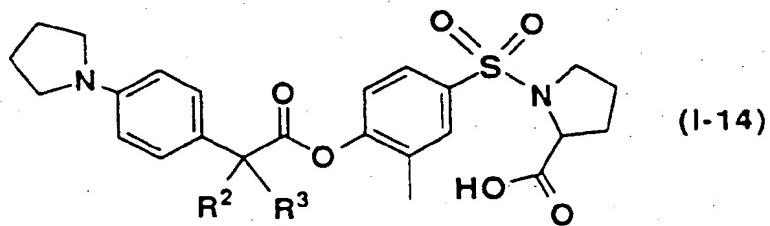
No.	$\text{R}^2 \text{ } \text{R}^3$	No.	$\text{R}^2 \text{ } \text{R}^3$
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 13



No.	$\text{R}^2 \text{---} \text{R}^3$	No.	$\text{R}^2 \text{---} \text{R}^3$
1	H --- H	8	
2	Me --- H	9	
3	Me --- Me	10	
4	Et --- Et	11	
5	MeO --- H	12	Cl --- H
6	Pr --- H	13	F ₃ C --- H
7	iPr --- H	14	

Table 14



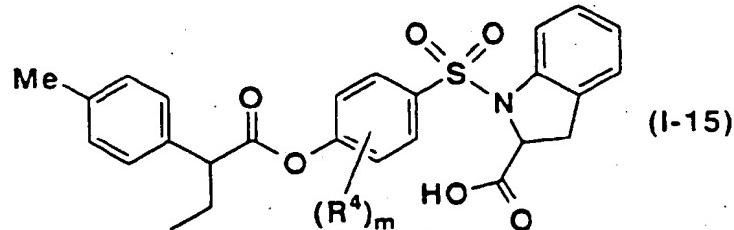
10

No.		No.	
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 15

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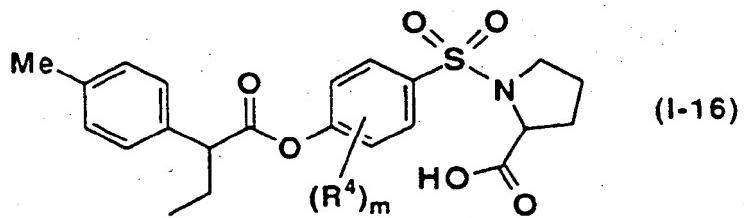
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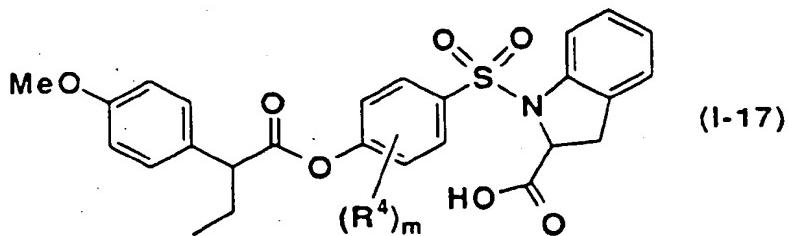
No.		No.	
1		5	
2		6	
3		7	
4			

Table 16



No.		No.	
1		5	
2		6	
3		7	
4			

Table 17



	No.		No.	
20				
25	1		5	
30	2		6	
35	3		7	
40	4			
45				

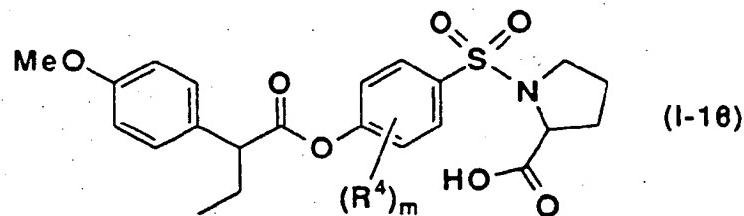
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Table 18

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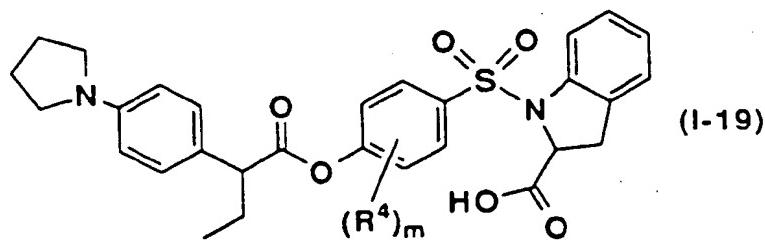
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	No.		No.	
1	1		5	
2	2		6	
3	3		7	
4	4			

Table 19

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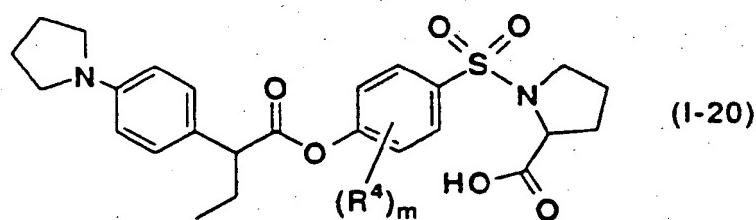
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	No.		No.	
1	1		5	
2	2		6	
3	3		7	
4	4			

Table 20



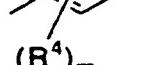
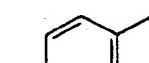
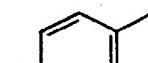
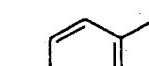
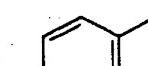
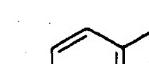
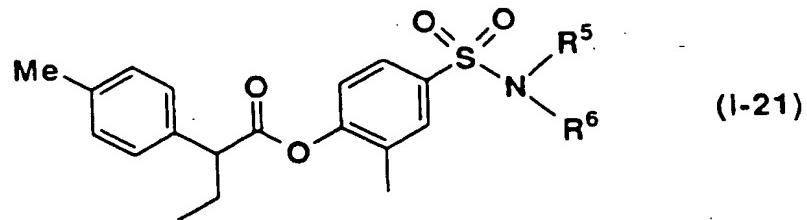
No. 1		No. 2	
1		5	
2		6	
3		7	
4			

Table 21

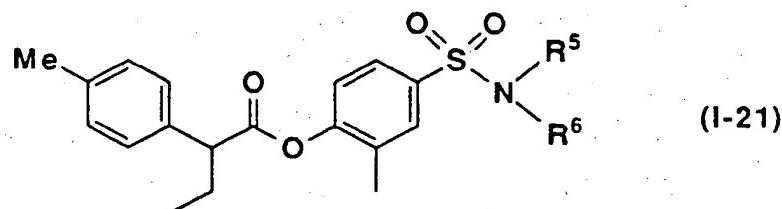


No.	$-N^R_5 R^6$	No.	$-N^R_5 R^6$
1	$-N^H R^5 R^6$	6	
2		7	
3		8	
4		9	
5		10	

Table 21 (continued)

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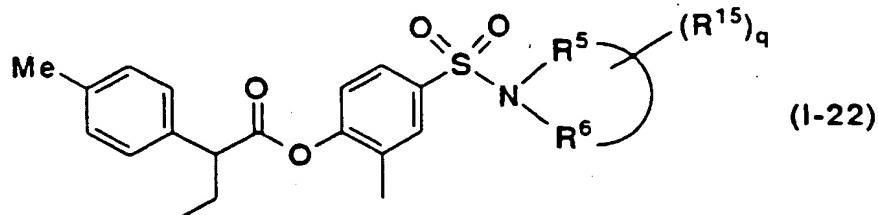
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No.	$-\text{N}^{\text{H}}\text{R}^5\text{R}^6$	No.	$-\text{N}^{\text{H}}\text{R}^5\text{R}^6$
11	$-\text{N}^{\text{H}}\text{CONH}_2$	16	$-\text{N}^{\text{H}}\text{C}_6\text{H}_4\text{CONHCH}_2\text{COOH}$
12	$-\text{N}^{\text{H}}\text{CH}_2\text{CH(OH)OH}$	17	$-\text{N}^{\text{H}}\text{C}_6\text{H}_4\text{C}_6\text{H}_5$
13	$-\text{N}^{\text{H}}\text{CH}_2\text{CH}_2\text{OH}$	18	$-\text{N}^{\text{H}}\text{CH}_2\text{CH}_2\text{C}_6\text{H}_4\text{N}$
14	$-\text{N}^{\text{H}}\text{C}_6\text{H}_4\text{C}_6\text{H}_4\text{N}=\text{N}$	19	$-\text{N}^{\text{H}}\text{CH}_2\text{CH}_2\text{N}$
15	$-\text{N}^{\text{H}}\text{C}_6\text{H}_4\text{CONHCH}_2\text{C}(=\text{O})\text{N}=\text{N}$	20	$-\text{N}^{\text{H}}\text{CH}_2\text{CH}_2\text{C}_6\text{H}_4\text{S}$

Table 22

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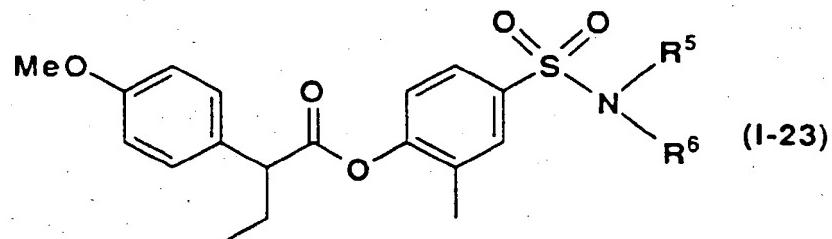
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No.	$-\text{N}^{\text{H}}(\text{R}^5)(\text{R}^6)_q$	No.	$-\text{N}^{\text{H}}(\text{R}^5)(\text{R}^6)_q$
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 23



No.	$-N(R^5)(R^6)$	No.	$-N(R^5)(R^6)$
1	$-NH-CH_2-COOH$	6	$-NH-CH_2-CH_2-CH_2-CH_2-CH_2-COOH$
2	$-NH-CH_2-CH_2-N(O)C_2H_5-COOH$	7	$-N(CH_2)_3$
3	$-NH-CH_2-CH(COOH)_2$	8	$-N(Me)-CH_2-O-CH_3$
4	$-NH-CH(CH_3)_2-COOH$	9	$-NH-CH_2-CH_2-O-C_6H_5$
5	$-NH-CH_2-CH_2-C_6H_4-OH-COOH$	10	$-NH-CH_2-CH_2-CH(Me)-Me$

Table 23 (continued)

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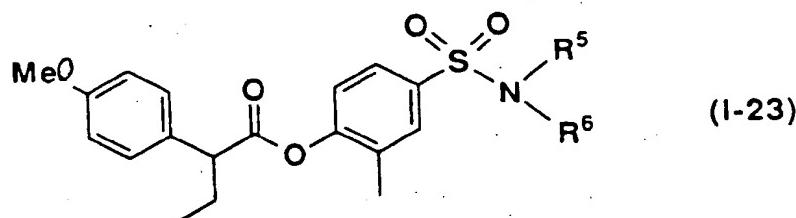
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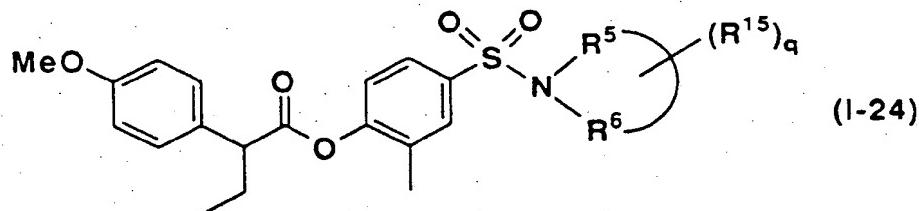


No.	$-\text{N}^{\text{H}}\text{--}\text{R}^5$	No.	$-\text{N}^{\text{H}}\text{--}\text{R}^5$
11	$-\text{N}^{\text{H}}\text{--}\text{CONH}_2$	16	$-\text{N}^{\text{H}}\text{--}\text{C}_6\text{H}_4\text{--}\text{CONH--CH}_2\text{COOH}$
12	$-\text{N}^{\text{H}}\text{--CH}_2\text{CH(OH)--CH}_2\text{OH}$	17	$-\text{N}^{\text{H}}\text{--C}_6\text{H}_4\text{--C}_6\text{H}_5$
13	$-\text{N}^{\text{H}}\text{--CH}_2\text{CH(OH)--CH}_2\text{OH}$	18	$-\text{N}^{\text{H}}\text{--CH}_2\text{CH}_2\text{--C}_6\text{H}_4\text{--N}=\text{C}_6\text{H}_5$
14	$-\text{N}^{\text{H}}\text{--C}_6\text{H}_4\text{--C}_6\text{H}_4\text{--N}=\text{N--N}$	19	$-\text{N}^{\text{H}}\text{--CH}_2\text{CH}_2\text{--N}(\text{CH}_2)_2\text{O}$
15	$-\text{N}^{\text{H}}\text{--C}_6\text{H}_4\text{--CONH--CH}_2\text{--C}_6\text{H}_4\text{--N}=\text{N--N}$	20	$-\text{N}^{\text{H}}\text{--CH}_2\text{CH}_2\text{--C}_6\text{H}_4\text{--S--C}_6\text{H}_4\text{--N}=\text{N}$

Table 24

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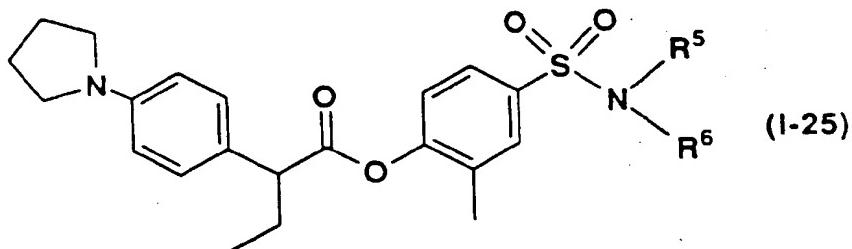
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No.	$-N(R^5)(R^6)(R^{15})_q$	No.	$-N(R^5)(R^6)(R^{15})_q$
1	$-N(\text{pyrrolidin-1-yl})\text{COOCH}_2\text{CONH}_2$	8	$-N(\text{pyrrolidin-1-yl})\text{COOCH}_2\text{CH}_2\text{OH}$
2	$-N(\text{pyrrolidin-1-yl})\text{COOCH}_2\text{N}(\text{CH}_3)_2$	9	$-N(\text{pyrrolidin-1-yl})\text{CONHCH}_2\text{COOH}$
3	$-N(\text{indolin-1-yl})\text{COOCH}_2\text{CONH}_2$	10	$-N(\text{indolin-1-yl})\text{COOCH}_2\text{CH}_2\text{OH}$
4	$-N(\text{indolin-1-yl})\text{COOCH}_2\text{N}(\text{CH}_3)_2$	11	$-N(\text{indolin-1-yl})\text{CONHCH}_2\text{COOH}$
5	$-N(\text{phenylthio})$	12	$-N(\text{pyrrolidin-1-yl})\text{OH}\text{COOH}$
6	$-N(\text{methylamino})\text{COOH}$	13	$-N(\text{azepan-1-yl})\text{O}$
7	$-N(\text{pyridin-2-yl})\text{COOH}$	14	$-N(\text{azepan-1-yl})\text{O}$

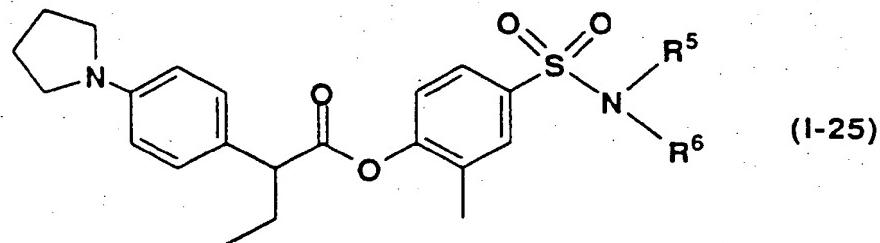
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Table 25



No.	$-N^{\text{H}}_{{\text{R}}^5}_{{\text{R}}^6}$	No.	$-N^{\text{H}}_{{\text{R}}^5}_{{\text{R}}^6}$
1	$-N^{\text{H}}_{{\text{R}}^5}_{{\text{R}}^6}$	6	
2		7	
3		8	
4		9	
5		10	

Table 25 (continued)



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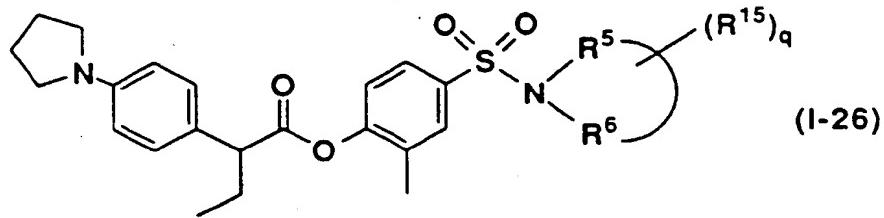
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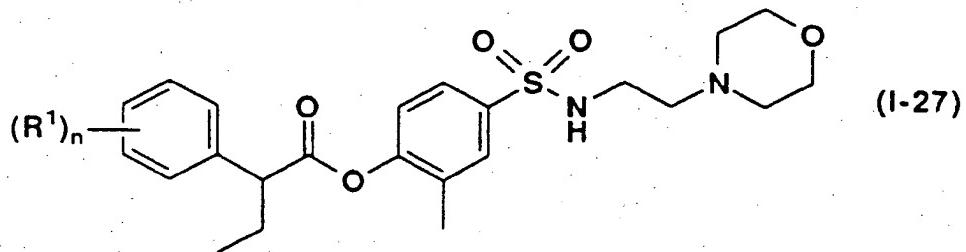
No.	$-N(R^5)R^6$	No.	$-N(R^5)R^6$
11	$-NH-CH_2CONH_2$	16	$-NH-C_6H_4-CH_2CONH-CH_2COOH$
12	$-NH-CH_2-CH(OH)-CH_2OH$	17	$-NH-C_6H_4-C_6H_5$
13	$-NH-CH_2-CH_2OH$	18	$-NH-CH_2-CH_2-pyridine$
14	$-NH-C_6H_4-C_6H_2(N=N)NH$	19	$-NH-CH_2-CH_2-N(CH_3)_2$
15	$-NH-C_6H_4-CH_2CONH-CH_2-C(=O)-N=N$	20	$-NH-CH_2-CH_2-C(=O)-N=N$

Table 26



No.	$-N(R^5)(R^6)_{(R^{15})_q}$	No.	$-N(R^5)(R^6)_{(R^{15})_q}$
1	$\begin{array}{c} \text{COO} \\ \\ -\text{N} \\ \\ \text{C}_5\text{H}_4 \\ \\ \text{COO} \end{array} \text{CONH}_2$	8	$\begin{array}{c} \text{COO} \\ \\ -\text{N} \\ \\ \text{C}_5\text{H}_4 \\ \\ \text{COO} \end{array} \text{CH}_2\text{CH}_2\text{OH}$
2	$\begin{array}{c} \text{COO} \\ \\ -\text{N} \\ \\ \text{C}_5\text{H}_4 \\ \\ \text{COO} \end{array} \text{CH}_2\text{CH}_2\text{N}_2$	9	$\begin{array}{c} \text{CONH} \\ \\ -\text{N} \\ \\ \text{C}_5\text{H}_4 \\ \\ \text{COOH} \end{array}$
3	$\begin{array}{c} \text{COO} \\ \\ -\text{N} \\ \\ \text{C}_5\text{H}_4 \\ \\ \text{COO} \end{array} \text{CONH}_2$	10	$\begin{array}{c} \text{COO} \\ \\ -\text{N} \\ \\ \text{C}_5\text{H}_4 \\ \\ \text{COO} \end{array} \text{CH}_2\text{CH}_2\text{OH}$
4	$\begin{array}{c} \text{COO} \\ \\ -\text{N} \\ \\ \text{C}_5\text{H}_4 \\ \\ \text{COO} \end{array} \text{CH}_2\text{CH}_2\text{N}_2$	11	$\begin{array}{c} \text{CONH} \\ \\ -\text{N} \\ \\ \text{C}_5\text{H}_4 \\ \\ \text{COOH} \end{array}$
5	$\begin{array}{c} \text{S} \\ \\ \text{C}_6\text{H}_4 \\ \\ -\text{N} \end{array}$	12	$\begin{array}{c} \text{OH} \\ \\ -\text{N} \\ \\ \text{C}_5\text{H}_4 \\ \\ \text{HOOC} \end{array}$
6	$\begin{array}{c} \text{NH} \\ \\ -\text{N} \\ \\ \text{C}_5\text{H}_4 \\ \\ \text{COOH} \end{array}$	13	$\begin{array}{c} \text{O} \\ \\ \text{C}_5\text{H}_4 \\ \\ -\text{N} \end{array}$
7	$\begin{array}{c} \text{COOH} \\ \\ -\text{N} \\ \\ \text{C}_5\text{H}_4 \end{array}$	14	$\begin{array}{c} \text{O} \\ \\ \text{C}_5\text{H}_4 \\ \\ -\text{N} \end{array}$

Table 27



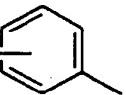
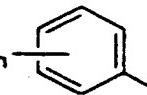
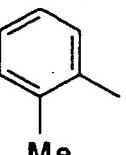
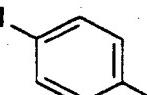
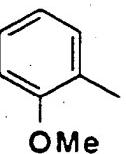
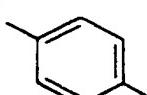
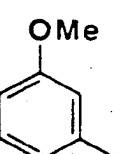
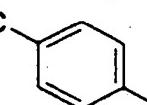
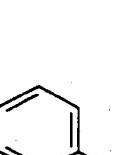
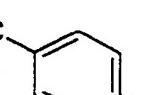
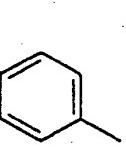
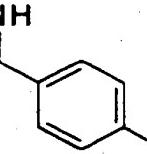
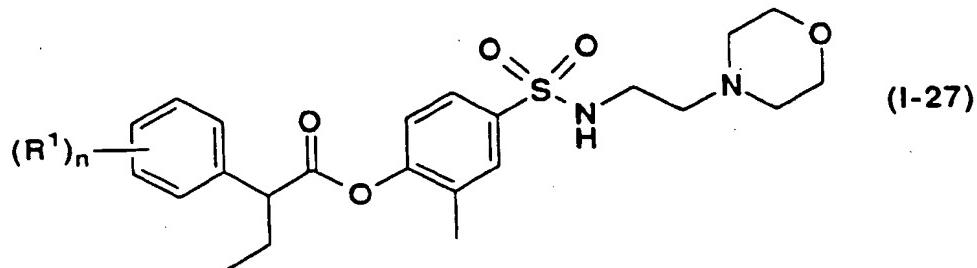
No.	$(R^1)_n$ — 	No.	$(R^1)_n$ — 
1		6	
2		7	
3		8	
4		9	
5		10	

Table 27 (continued)

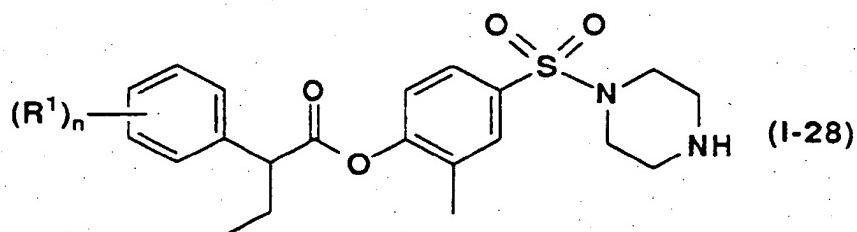


No.	$(R^1)_n-$ phenyl	No.	$(R^1)_n-$ phenyl
11	$\text{HOOC}-\text{C}_6\text{H}_4-\text{CH}_3$	15	$t\text{BuOOC}-\text{N}-\text{C}_6\text{H}_4-\text{CH}_3$
12	$\text{MeOOC}-\text{C}_6\text{H}_4-\text{CH}_3$	16	$\text{H}_2\text{N}-\text{C}(=\text{O})-\text{NH}-\text{C}_6\text{H}_4-\text{CH}_3$
13	$\text{Me}-\text{N}(\text{Me})-\text{C}_6\text{H}_4-\text{CH}_3$	17	$\text{H}_2\text{N}-\text{C}(=\text{O})-\text{NH}-\text{C}_6\text{H}_4-\text{CH}_3$
14	$\text{Me}-\text{C}(=\text{O})-\text{NH}-\text{C}_6\text{H}_4-\text{CH}_3$	18	$\text{HN}-\text{C}_4\text{H}_9-\text{N}-\text{C}_6\text{H}_4-\text{CH}_3$

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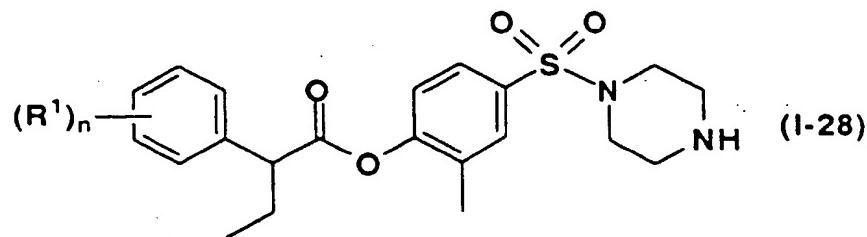
55

Table 28



No.	$(R^1)_n - \text{C}_6\text{H}_4 - \text{CH}_3$	No.	$(R^1)_n - \text{C}_6\text{H}_4 - \text{CH}_3$
1		6	
2		7	
3		8	
4		9	
5		10	

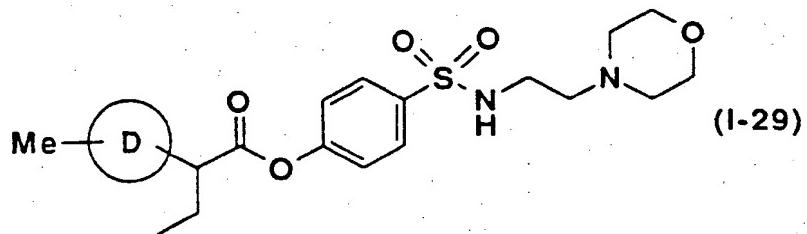
Table 28 (continued)



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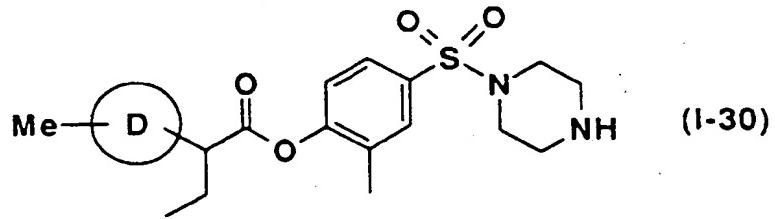
No.	(R ¹) _n -	No.	(R ¹) _n -
20	11	15	
25	12	16	
30	13	17	
35	14	18	
40			
45			
50			

Table 29



No.	$\text{Me} - \text{C}(=\text{O}) - \text{D}$	No.	$\text{Me} - \text{C}(=\text{O}) - \text{D}$
1		6	
2		7	
3		8	
4		9	
5		10	

Table 30



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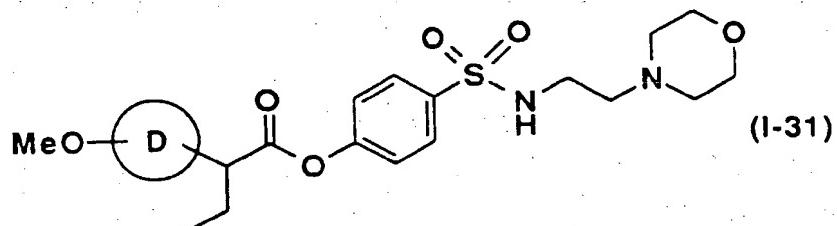
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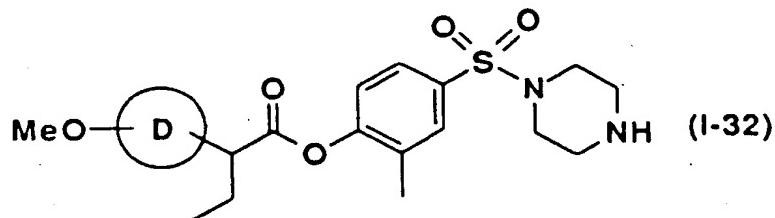
No.	Me — D	No.	Me — D
1		6	
2		7	
3		8	
4		9	
5		10	

Table 31



No.	MeO—D—	No.	MeO—D—
1		6	
2		7	
3		8	
4		9	
5		10	

Table 32



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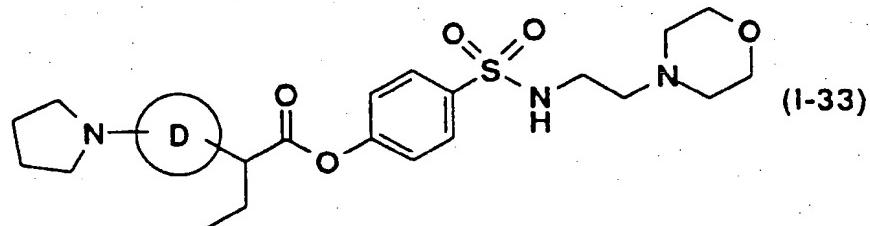
45

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	No. MeO-D	No. MeO-D
1		
2		
3		
4		
5		

Table 33



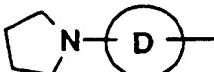
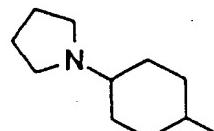
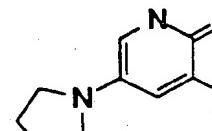
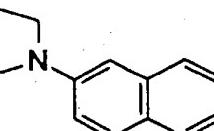
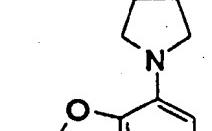
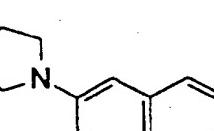
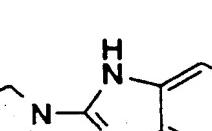
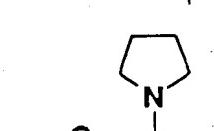
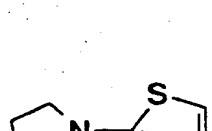
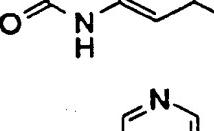
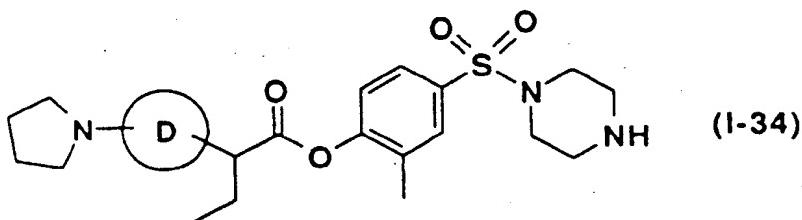
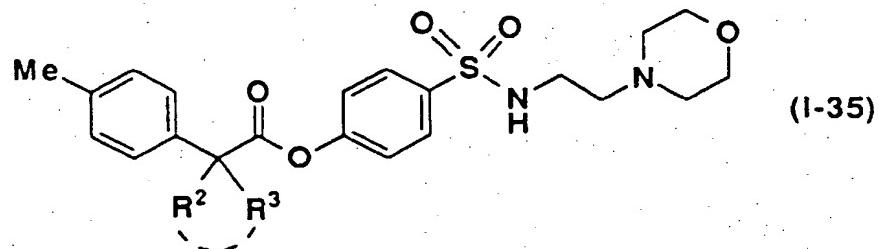
No.		No.	
1		6	
2		7	
3		8	
4		9	
5		10	

Table 34



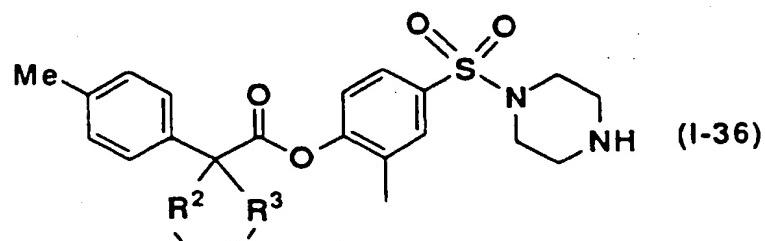
No.		No.	
1		6	
2		7	
3		8	
4		9	
5		10	

Table 35



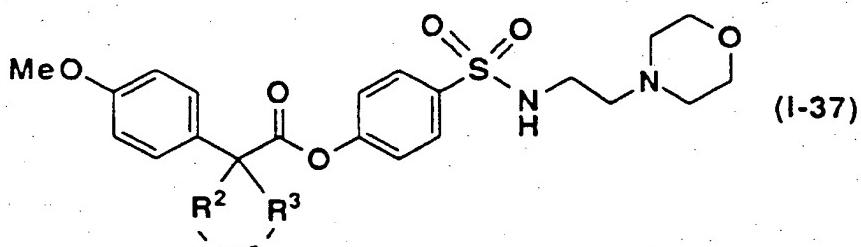
No.	$\begin{array}{c} \diagup \\ R^2 \\ \diagdown \\ R^3 \end{array}$	No.	$\begin{array}{c} \diagup \\ R^2 \\ \diagdown \\ R^3 \end{array}$
1	$\begin{array}{c} \diagup \\ H \\ \diagdown \\ H \end{array}$	8	$\begin{array}{c} \diagup \\ \diagdown \\ \diagup \\ \diagdown \end{array}$
2	$\begin{array}{c} \diagup \\ Me \\ \diagdown \\ H \end{array}$	9	$\begin{array}{c} \diagup \\ \diagdown \\ \diagup \\ \diagdown \end{array}$
3	$\begin{array}{c} \diagup \\ Me \\ \diagdown \\ Me \end{array}$	10	$\begin{array}{c} \diagup \\ \diagdown \\ \diagup \\ \diagdown \end{array}$
4	$\begin{array}{c} \diagup \\ Et \\ \diagdown \\ Et \end{array}$	11	$\begin{array}{c} \diagup \\ \diagdown \\ \diagup \\ \diagdown \end{array}$
5	$\begin{array}{c} \diagup \\ MeO \\ \diagdown \\ H \end{array}$	12	$\begin{array}{c} \diagup \\ Cl \\ \diagdown \\ H \end{array}$
6	$\begin{array}{c} \diagup \\ Pr \\ \diagdown \\ H \end{array}$	13	$\begin{array}{c} \diagup \\ F_3C \\ \diagdown \\ H \end{array}$
7	$\begin{array}{c} \diagup \\ iPr \\ \diagdown \\ H \end{array}$	14	$\begin{array}{c} \diagup \\ \text{Phenyl} \\ \diagdown \\ H \end{array}$

Table 36



No.		No.	
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

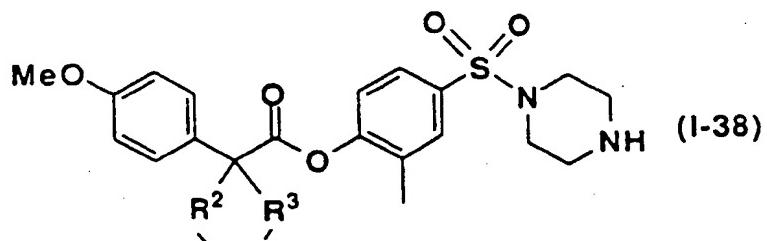
Table 37



No.	$\begin{array}{c} \diagup \\ R^2 \\ \diagdown \\ \text{---} \\ \diagdown \\ R^3 \end{array}$	No.	$\begin{array}{c} \diagup \\ R^2 \\ \diagdown \\ \text{---} \\ \diagdown \\ R^3 \end{array}$
1	$\begin{array}{c} \diagup \\ \text{H} \\ \diagdown \\ \text{H} \end{array}$	8	$\begin{array}{c} \diagup \\ \text{H} \\ \diagdown \\ \text{H} \end{array}$
2	$\begin{array}{c} \diagup \\ \text{Me} \\ \diagdown \\ \text{H} \end{array}$	9	$\begin{array}{c} \diagup \\ \text{H} \\ \diagdown \\ \text{H} \end{array}$
3	$\begin{array}{c} \diagup \\ \text{Me} \\ \diagdown \\ \text{Me} \end{array}$	10	$\begin{array}{c} \diagup \\ \text{H} \\ \diagdown \\ \text{H} \end{array}$
4	$\begin{array}{c} \diagup \\ \text{Et} \\ \diagdown \\ \text{Et} \end{array}$	11	$\begin{array}{c} \diagup \\ \text{H} \\ \diagdown \\ \text{H} \end{array}$
5	$\begin{array}{c} \diagup \\ \text{MeO} \\ \diagdown \\ \text{H} \end{array}$	12	$\begin{array}{c} \diagup \\ \text{Cl} \\ \diagdown \\ \text{H} \end{array}$
6	$\begin{array}{c} \diagup \\ \text{Pr} \\ \diagdown \\ \text{H} \end{array}$	13	$\begin{array}{c} \diagup \\ \text{F}_3\text{C} \\ \diagdown \\ \text{H} \end{array}$
7	$\begin{array}{c} \diagup \\ \text{iPr} \\ \diagdown \\ \text{H} \end{array}$	14	$\begin{array}{c} \diagup \\ \text{H} \\ \diagdown \\ \text{H} \end{array}$

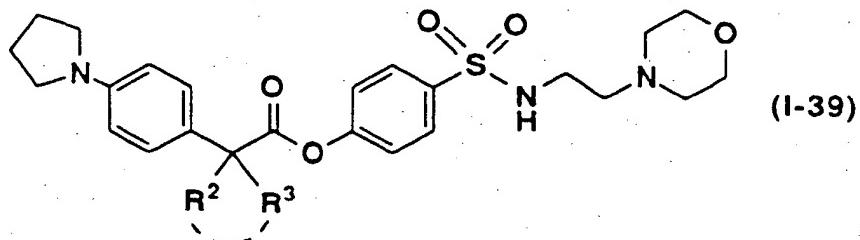
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Table 38



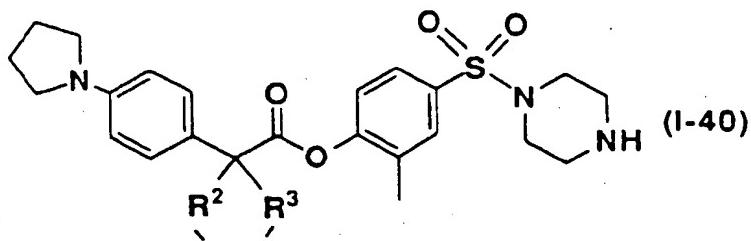
No.		No.	
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 39

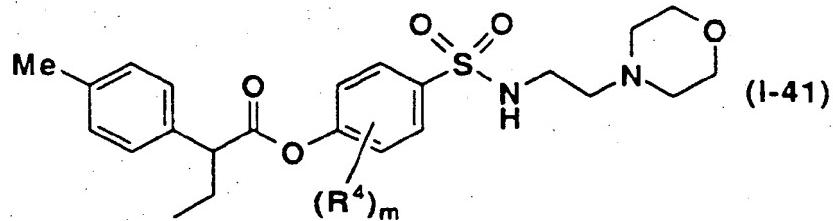


No.	R^2	R^3	No.	R^2	R^3
1	H	H	8		
2	Me	H	9		
3	Me	Me	10		
4	Et	Et	11		
5	MeO	H	12	Cl	H
6	Pr	H	13	F_3C	H
7	iPr	H	14		

Table 40



No.	R^2	R^3	No.	R^2	R^3
1	H	H	8		
2	Me	H	9		
3	Me	Me	10		
4	Et	Et	11		
5	MeO	H	12	Cl	H
6	Pr	H	13	F_3C	H
7	iPr	H	14		

Table 41

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No.		No.	
1		5	
2		6	
3		7	
4			

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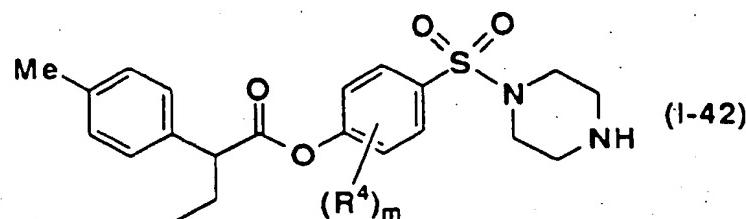
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Table 42

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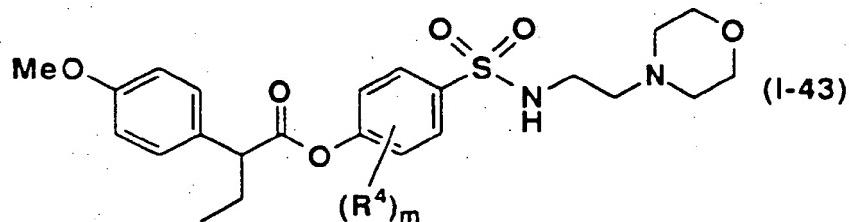
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No.		No.	
1		5	
2		6	
3		7	
4			

Table 43



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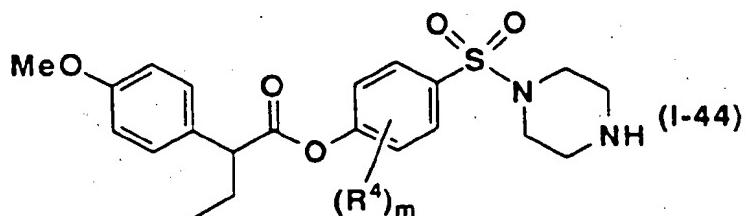
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No.		No.	
1		5	
2		6	
3		7	
4			

Table 44



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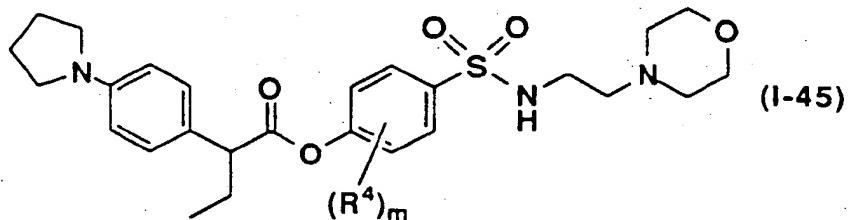
55

No.		No.	
1		5	
2		6	
3		7	
4			

Table 45

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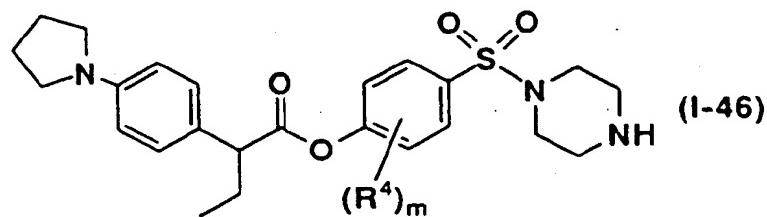
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No.		No.	
1		5	
2		6	
3		7	
4			

Table 46

15

No.		No.	
1		5	
2		6	
3		7	
4			

20

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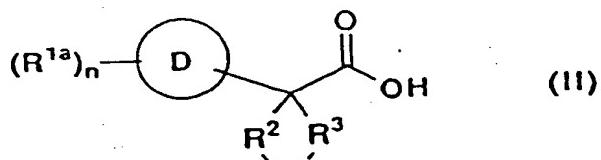
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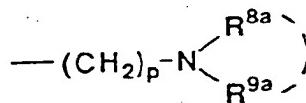
The compounds of formula (I), of the present invention, may be prepared by esterifying a compound of formula (II)

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wherein R^{1a} is C1-8 alkyl, C1-8 alkoxy, hydroxy, protected hydroxy, keto, nitro, halogen atom, trihalomethyl, cyano, amidino, -COOR^{7a} (in which R^{7a} is C1-8 alkyl or benzyl), or

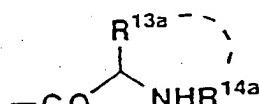
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(in which p is as hereinbefore defined, R^{8a} and R^{9a} each, independently, is hydrogen atom (with the proviso that, R^{8a} and R^{9a} do not represent hydrogen atom at the same time), t-butoxycarbonyl, benzyloxycarbonyl, C1-4 alkyl, C2-5 acyl, -COOR^{10a} (in which R^{10a} is C1-8 alkyl or benzyl), -CONR¹¹R¹² (in which R¹¹ and R¹² are as hereinbefore defined), or

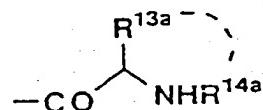
15



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(in which

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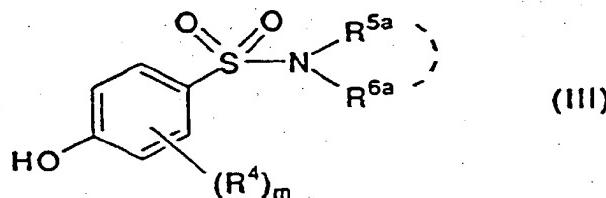


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is a protected α-amino acid residue), or R^{8a} and R^{9a}, taken together with the nitrogen atom to which they are attached represent an aliphatic heterocyclic ring which is unsubstituted or substituted by C1-4 alkyl or phenyl C1-4 alkyl, and the other symbols are as hereinbefore defined with a compound of formula (III)

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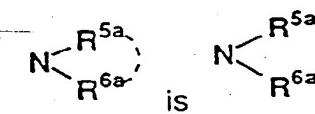
40



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wherein

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(in which R^{5a} and R^{6a} each, independently, is

- 1) hydrogen atom (with the proviso that, R^{5a} and R^{6a} do not represent hydrogen atom at the same time),
- 2) hydroxy,
- 3) hydroxy protected by a protecting group which is removable under acid conditions,
- 4) t-butoxycarbonyl,

- 5) benzyloxycarbonyl,
 6) C1-8 alkyl,
 7) C1-8 alkoxy,
 8) phenyl C1-4 alkoxy,

5 9) amidino,
 10) -M-R^{16a} (in which M is as hereinbefore defined, and R^{16a} is

i) -NR^{17a}R^{18a} (in which R^{17a} and R^{18a} each, independently, is hydrogen atom (with the proviso that, R^{17a} and R^{18a} do not represent hydrogen atom at the same time), t-butoxycarbonyl, benzyloxycarbonyl or C1-4 alkyl), ii) -CONR¹⁹R²⁰ (in which R¹⁹ and R²⁰ are as hereinbefore defined),

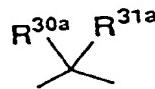
10 iii)



15 (in which all the symbols are as hereinbefore defined), iv) heterocyclic ring, unsubstituted or substituted by 1 to 4 substituents selected from C1-4 alkyl, C1-4 alkoxy, hydroxy, phenyl C1-4 alkyl, -COOR²⁶ (in which R²⁶ is as hereinbefore defined), hydroxy C1-4 alkyl in which hydroxy is protected by a protecting group which is removable under acid conditions or C2-4 alkoxyalkyl).

20 11) C1-8 alkyl substituted by one or two of -OR^{27a} (in which R^{27a} is hydrogen atom, C1-4 alkyl, C2-4 alkoxyalkyl, t-butyldimethylsilyl, THP, benzyl, or C2-4 alkyl substituted by -OH^{28a} (in which R^{28a} is hydrogen atom, C2-4 alkoxyalkyl, t-butyldimethylsilyl, THP or benzyl)),
 12) -J^a-COOR²⁹ (in which R²⁹ is as hereinbefore defined, J^a is a single bond, -(CH₂)_s- or

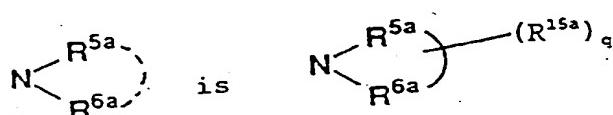
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(in which s is as hereinbefore defined,
 R^{30a} and R^{31a} each, independently, is i) hydrogen atom, ii) C1-8 alkyl, iii) -COOR³² (in which R³² is as hereinbefore defined), iv) carbocyclic or heterocyclic ring, unsubstituted or substituted by one or more substituents selected from defined, v) C1-8 alkyl substituted by one or more substituents selected from hydroxy, protected hydroxy, halogen atom, nitrile, guanidino and amidino, C1-4 alkyl, C1-4 alkoxyalkyl, amino, nitro, hydroxy, protected hydroxy, halogen atom, nitrile, guanidino and amidino, or v) C1-8 alkyl substituted by one or more substituents selected from hydroxy, protected hydroxy, -COOR³³ (in which R³³ is as hereinbefore defined), -NR^{34a}R^{35a} (in which R^{34a} and R^{35a} each, independently, is hydrogen atom (with the proviso that, R^{34a} and R^{35a} do not represent hydrogen atom at the same time), t-butoxycarbonyl, benzyloxycarbonyl or C1-4 alkyl), carbocyclic or, heterocyclic ring, unsubstituted or substituted by one or more substituents selected from C1-4 alkyl, C1-4 alkoxyalkyl, protected amino, nitro, hydroxy, protected hydroxy, halogen atom, nitrile, guanidino and amidino, with the proviso that a carbon atom of C1-8 alkyl may be replaced by a sulfur atoms, or

45



50 in which R^{5a} and R^{6a}, taken together with the nitrogen atom to which they are attached represent a heterocyclic ring, q is as hereinbefore defined,
 R^{15a} is
 1) hydroxy,
 2) hydroxy protected by a protecting group which is removable under acid conditions,
 3) keto,
 4) protected keto,
 5) C1-4 alkyl,
 6) C1-4 alkoxy,
 7) phenyl,

- 8) phenoxy,
- 9) phenyl C1-4 alkyl,
- 10) phenyl C1-4 alkoxy,
- 11) nitro.

5 12) -COOR^{36a} (in which R^{36a} is hydrogen atom, C1-8 alkyl, C1-4 alkyl substituted by -CONR³⁷R³⁸ (in which R³⁷ and R³⁸ are as hereinbefore defined, C1-4 alkyl substituted by -NR^{39a}R^{40a} (in which R^{39a} and R^{40a} each, independently, is hydrogen atom (with the proviso that, R^{39a} and R^{40a} do not represent hydrogen atom at the same time), t-butoxycarbonyl, benzyloxycarbonyl or C1-4 alkyl), C1-4 alkyl substituted by -OR^{41a} (in which R^{41a} is C2-4 alkyl substituted by -OR^{42a} (in which R^{42a} is hydrogen atom, C2-4 alkoxyalkyl or benzyl)) or C1-4 alkyl substituted by protected piperazino ring).

10 13)-NR^{43a}R^{44a} (in which R^{43a} and R^{44a} each, independently, is hydrogen atom (with the proviso that, R^{43a} and R^{44a} do not represent hydrogen atom at the same time), t-butoxycarbonyl, benzyloxycarbonyl, C1-4 alkyl or C2-5 acyl),

15 14) -CONR^{45a}R^{46a} (in which R^{45a} and R^{46a} each, independently, is hydrogen atom, C1-4 alkyl, hydroxy, hydroxy protected by a protecting group which is removable under acid conditions, phenyl C1-4 alkoxy or C1-4 alkyl substituted by hydroxy, protected hydroxy or -COOR^{47a} (in which R^{47a} is hydrogen atom, C1-8 alkyl or benzyl)),

20 15) C1-4 alkyl substituted by one or more substituents selected from hydroxy, protected hydroxy, -COOR^{48a} (in which R^{48a} is hydrogen atom, C1-8 alkyl or benzyl), -NR^{49a}R^{50a} (in which R^{49a} and R^{50a} each, independently, is hydrogen atom (with the proviso that, R^{49a} and R^{50a} do not represent hydrogen atom at the same time), t-butoxycarbonyl, benzyloxycarbonyl or C1-4 alkyl), or 5- or 6-membered heterocyclic ring containing one or two nitrogen atoms,

25 16) 5- or 6-membered heterocyclic ring containing one or two nitrogen atoms,

30 17) halogen atom,

35 18) -CHO protected by a protecting group which is removable under acid conditions, or

40 19) -NR^{51a}-COOR^{52a} (in which R^{51a} and R^{52a} each, independently, is hydrogen atom or C1-8 alkyl), and the other symbols are as hereinbefore defined, or

45 may be prepared by esterifying a compound of formula (II) with a compound of formula (III) to obtain a compound having protected group(s) and then eliminating the protecting group(s) (e.g. by hydrolysis of t-butylester, treatment with acid and/or hydrogenolysis), or may be prepared by esterifying a compound of formula (II) with a compound of formula (III), if necessary, eliminating the protecting groups to obtain a compound having R¹⁵ represent C1-4 alkyl substituted by hydroxy, and then subjecting to sulfuric acid esterification; and optionally converting a compound of formula (I) thus obtained into a non-toxic salt, acid addition salt or solvate thereof.

Protected hydroxy means, for example, hydroxy protected by a protecting group which is removable under acid conditions (e.g. C2-4 alkoxyalkyl, t-butyldimethylsilyl, tetrahydropyran (THP), triphenylmethyl) or hydroxy protected by a protecting group which is removable by hydrogenation (e.g. benzyl).

Hydroxy protected by a protecting group which is removable under acid conditions means, for example, hydroxy group protected by C2-4 alkoxyalkyl, t-butyldimethylsilyl, tetrahydropyran (THP) or triphenylmethyl.

Protected amino acid, α -amino acid or piperazino ring means, for example, amino acid, α -amino acid or piperazino ring protected by t-butoxycarbonyl (Boc) or benzyloxycarbonyl (Cbz).

-CHO protected by a protecting group which is removable under acid conditions means, for example, -CHO protected by acetal (e.g. dimethylacetal or diethylacetal or ketal (e.g. ethylenedioxyketal or trimethylenedioxyketal)).

The above esterification is known *per se* and can be carried out by methods for example:

- (1) using an acid halide,
- (2) using a mixed acid anhydride,
- (3) using a condensing agent.

Each of these methods can be carried out, for example, as follows:

(1) the method using an acid halide may be carried out, for example, by reacting a carboxylic acid with an acid halide (e.g., oxalyl chloride or thionyl chloride) in an inert organic solvent (e.g., chloroform, methylene chloride, diethyl ether or tetrahydrofuran) or without a solvent at from -20°C to the reflux temperature of the solvent, and then by reacting the acid halide obtained with a corresponding alcohol in the presence of a tertiary amine (e.g. pyridine, triethylamine, dimethylaniline or dimethylaminopyridine) in an inert organic solvent (e.g. chloroform, methylene chloride, diethyl ether or tetrahydrofuran), at a temperature of from 0°C to 40°C.

(2) the method using a mixed acid anhydride may be carried out, for example, by reacting a carboxylic acid and an acid halide (e.g. pivaloyl chloride, tosyl chloride or mesyl chloride) or an acid derivative (e.g. ethyl chloroformate or isobutyl chloroformate) in the presence of a tertiary amine (e.g. pyridine, triethylamine, dimethylaniline or dimethylaminopyridine) in an inert organic solvent (e.g. chloroform, methylene chloride, diethyl ether or tetrahydrofuran)

or without a solvent at a temperature of from 0°C to 40°C, and then by reacting the mixture of acid anhydride obtained with a corresponding alcohol in an inert organic solvent (e.g. chloroform, methylene chloride, diethyl ether or tetrahydrofuran), at a temperature of from 0°C to 40°C,

- 5 (3) the method using a condensing agent (e.g., 1,3-dicyclohexyl carbodiimide (DCC), 1-ethyl-3-[3-(dimethylamino) propyl]carbodiimide (EDC) or 2-chloro-1-methylpyridinium iodide) may be carried out, for example, by reacting a carboxylic acid with a corresponding alcohol using a condensing agent in the presence or absence of a tertiary amine (e.g. pyridine, triethylamine, dimethylaniline or dimethylaminopyridine) in an inert organic solvent (e.g., chloroform, methylene chloride, dimethyl formamide or diethyl ether) or without a solvent at a temperature of from 0°C to 10°C.

The reactions (1), (2) and (3) hereinbefore described may be preferably carried out in an atmosphere of inert gas (e.g. argon or nitrogen) under anhydrous conditions.

15 The hydrolysis of t-butylester group or the reaction resulting from treatment with acid (e.g. elimination of C2-4 alkoxyalkyl, t-butoxycarbonyl or dimethylacetal) is known *per se* and may be carried out, for example, by using an organic acid (e.g. trifluoroacetic acid) or an inorganic acid (e.g. hydrochloric acid), or a mixture thereof, in an inert organic solvent (e.g. methylene chloride, chloroform, methanol, dioxane, ethyl acetate or anisole) at a temperature of from 0°C to 90°C.

20 The hydrogenolysis is known *per se*, and may be carried out, for example, in an inert solvent [such as an ether (e.g. tetrahydrofuran, dioxane, diethoxyethane or diethyl ether), an alcohol (e.g., methanol or ethanol), a benzene analogue (e.g. benzene or toluene), a ketone (e.g. acetone or methyl ethyl ketone), a nitrile (e.g. acetonitrile), an amine (e.g. dimethylformamide), water, ethyl acetate, acetic acid or a mixture of two or more of them], in the presence of a hydrogenation catalyst (e.g., palladium on activated carbon, palladium black, palladium, palladium hydroxide on carbon, platinum oxide, nickel or Raney nickel (registered trade mark)), in the presence or absence of an inorganic acid (e.g. hydrochloric acid, sulfuric acid, hypochlorous acid, boric acid or tetrafluoroboric acid) or an organic acid (e.g., acetic acid, p-toluenesulfonic acid, oxalic acid, trifluoroacetic acid or formic acid), at ordinary or elevated pressure under an atmosphere of hydrogen, at a temperature of from 0°C to 200°C. When using an acid, its salt may be used at the same time.

25 The sulfuric acid esterification is known *per se*, and may be carried out, for example, by reacting sulfur trioxide pyridine complex in the presence of a tertiary amine (e.g. pyridine) at a temperature of from 0°C to 40°C.

30 The compounds of formulae (II) and (III) used as starting materials may be prepared by the methods of the following Scheme 1 or by methods known *per se* or are commercially available compounds. For example, 2-phenylbutanoic acid is commercially available. The compounds may also be prepared by the methods described in the Examples of the present specification.

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Scheme 1

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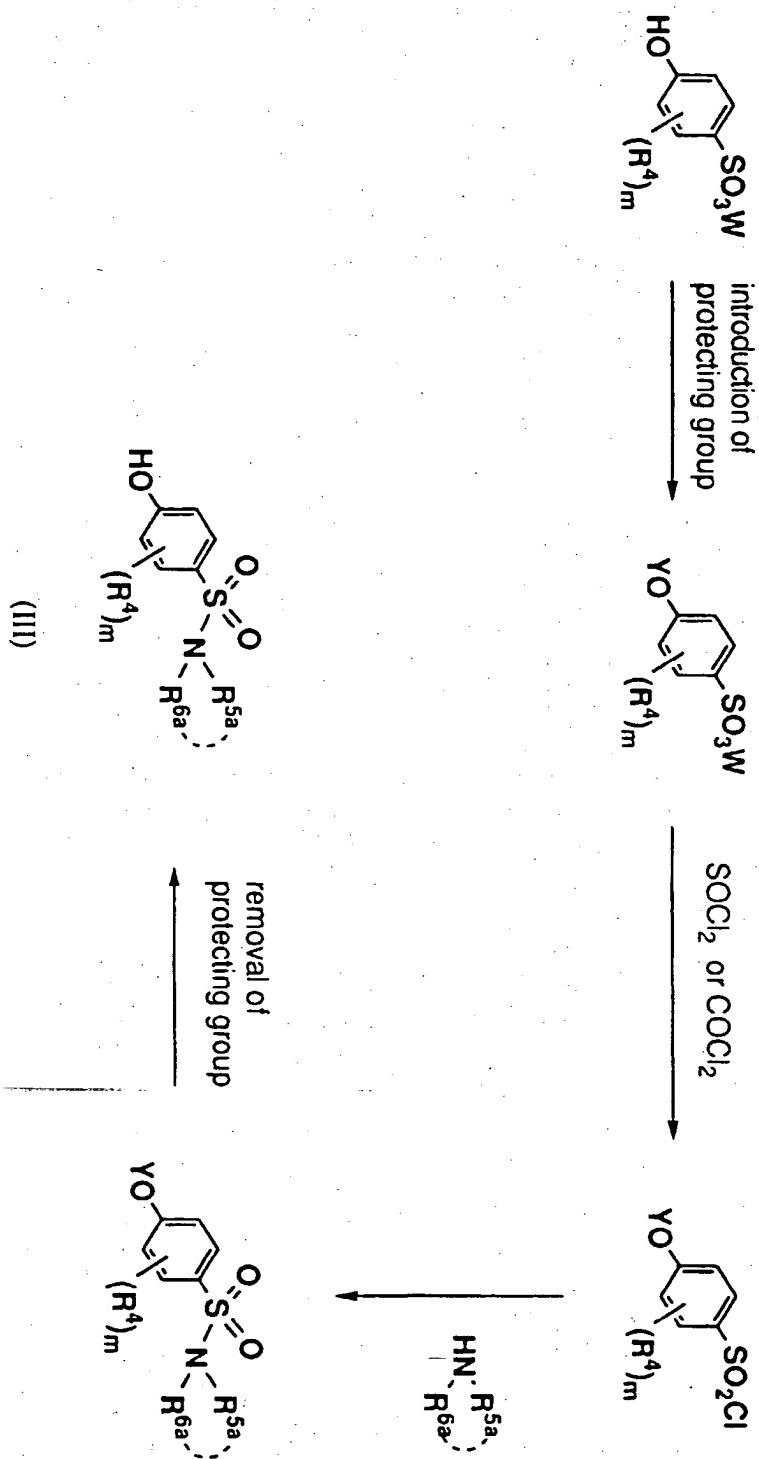
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In Scheme 1 hereinbefore described

W is an alkali metal.

Y is benzyl, benzyloxycarbonyl, or a protecting group which may be removed under acid conditions (e.g. C2-4 alkoxyalkyl, t-butyldimethylsilyl, tetrahydropyran (THP) or triphenylmethyl), and the other symbols are as hereinbefore defined.

5 It has been confirmed that the compounds of the formula (I), of the present invention have inhibitory activities on elastase. For example, in laboratory tests the following results were obtained.

(1) Inhibitory effects on human polymorphonuclear elastase

10 A mixture with 0.5 ml of 0.2 mM HEPES buffer (pH 8.0), 0.2 ml of 2.5 M NaCl, 0.1 ml of 1 % polyethyleneglycol 6000, 0.13 ml of distilled water, test compound dissolved in 0.01 ml of dimethylsulfoxide (DMSO) and 0.05 ml of 0.8 Unit/ml human polymorphonuclear elastase (HSE) was preincubated at 37 °C for 20 min. 5 mM of Meo-Suc-Ala-Ala-Pro-Val-pNA (DMSO solution, 0.01ml) was then added to the above mixture and was incubated at 37°C for 5 min. The reaction was terminated by 0.1 ml of 50% acetic acid and the p-nitroanilide (pNA) released was measured spectro-
15 photometrically at 405 nM. Percent inhibition of a compound was calculated by the following equation.

$$\text{Inhibition (\%)} = 1 - \frac{\text{delta OD(test-blank)}}{\text{delta OD(control-blank)}} \times 100$$

20 Results are shown in Table 47.

[Table 47]

	Example No.	IC ₅₀ (μM)
25	1(16)	0.017
	1(40)	0.019
	1(56)	0.014
	1(78)	0.0080
	1(130)	0.022
30	1(139)	0.024
	2	0.055
	2(1)	0.012
	2(42)	0.013
	2(62)	0.0068
35	2(69)	0.011
	2(77)	0.018
	2(111)	0.0097
	2(120)	0.023
	2(157)	0.008
40	2(173)	0.014
	2(179)	0.049
	2(197)	0.010
	2(274)	0.012
	2(276)	0.0093

(2) Inhibitory effects on human polymorphonuclear elastase induced lung hemorrhage in hamster

50 A test compound suspended in 0.5 % Carboxymethylcellulose or 80 % Polyethyleneglycol, 400 or 2 % Tween 80 was administered orally to a group of 5 Syrian hamsters. At 60 min after the administration, 10 U/0.1 ml of HSE was injected intratracheally via surgically exposed trachea under pentobarbital anesthesia (60 mg/kg, i.p.) to induce lung injury. At 60 min after the injection, hamsters were bled to sacrifice and subjected to bronchoalveolar lavage with 2.5 ml of saline and recovered lavage solution (BALF). The recovered BALF (0.5 ml) was diluted by 4 times with 2 % aqueous solution sodium carbonate and sonicated for 10 sec. The lavage fluid was further diluted by 2.5 times with 2% aqueous solution sodium carbonate and the amount of blood in BALF was calculated from absorbance at 414 nM using standard curve.

Results are shown in Table 48 and 49.

[Table 48]

Example No.	inhibition at 500 mg/kg (%)
1(68)	51
1(90)	65
2	81
2(42)	67
2(69)	83

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[Table 49]

Example No.	ED ₅₀
1(139)	192 mg/kg
2(274)	132 mg/kg
2(276)	73 mg/kg

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The above experiments show that compounds of the present invention possess inhibitory activity on elastase, even when administered orally.

The toxicity of the compounds of the present invention is very low. Therefore, the compounds of the present invention may be considered to be sufficiently safe and suitable for pharmaceutical use.

25

The compounds of the formula (I), of the present invention, and non-toxic salts and acid addition salts thereof, possess inhibitory activity on elastase. Accordingly, they are useful for the treatment and/or prevention of diseases induced by an abnormal enhancement of the degradation of elastin, collagen fiber and/or proteoglycan, resulting from the action of elastase on a mammalian animal, especially a human (e.g. chronic obstructive pulmonary disease such as emphysema, rheumatoid arthritis, atherosclerosis, adult respiratory distress syndrome (ARDS), glomerular nephritis, myocardial infarction, idiopathic ulcerative colitis or gingivitis).

30

For the purpose above described, the compounds of the formula (I), of the present invention, or non-toxic salts, acid addition salts or solvates thereof may normally be administered systemically or locally usually by oral or parenteral administration.

35

The doses to be administered are determined depending upon, for example, age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment. In the human adult, the doses per person are generally from 1 mg to 1000 mg, by oral administration, up to several times per day, or from 0.1 mg to 100 mg, by parenteral administration up to several times per day, or by continuous administration for from 1 to 24 hrs. per day from vein.

As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

40

The compounds of the present invention may be administered in the form of, for example, solid compositions, liquid compositions or other compositions for oral administration, injections, liniments or suppositories for parenteral administration.

45

Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules. Capsules include hard capsules and soft capsules.

In such compositions, one or more of the active compound(s) may be admixed with at least one inert diluent (such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone or magnesium metasilicate aluminate). The compositions may also comprise, as is normal practice, additional substances other than inert diluents: e.g. lubricating agents (such as magnesium stearate), disintegrating agents (such as cellulose calcium glycolate), stabilizing agents (such as lactose), and agents to assist dissolution (such as glutamic acid or asparagine acid).

50

The tablets or pills may, if desired, be coated with a film of gastric or enteric material (such as sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phthalate), or be coated with two or more films. And further, coating may include containment within capsules of absorbable materials such as gelatin.

55

Liquid compositions for oral administration include pharmaceutically-acceptable solutions, emulsions, suspensions, syrups and elixirs. In such compositions, one or more of the active compound(s) contained in inert diluent(s) commonly used in the art (e.g. purified water or ethanol). Besides inert diluents, such compositions may also comprise adjuvants (such as wetting agents or suspending agents, sweetening agents, flavouring agents, perfuming agents, and preserving agents).

Other compositions for oral administration include spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s). Spray compositions may comprise additional substances other than inert diluents: e.g. stabilizing agents (such as sodium sulfate), isotonic buffers (such as sodium chloride, sodium citrate or citric acid). For preparation of such spray compositions, for example, the method described in the United States Patent No. 2868691 or 3095355 may be used.

Injections for parenteral administration include sterile aqueous or non aqueous solutions, suspensions and emulsions. In such compositions, one or more active compound(s) may be admixed with at least one inert aqueous diluent(s) (e.g. distilled water for injection or physiological salt solution) or inert non-aqueous diluent(s) (e.g. propylene glycol, polyethylene glycol, olive oil, ethanol or POLYSORBATE80 (registered trade mark)).

Injections may comprise additional ingredients other than inert diluents: e.g. preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agents (e.g. lactose), assisting agents such as agents to assist dissolution (e.g. glutamic acid or asparagine acid).

They may be sterilized for example, by filtration through a bacteria-retaining filter, by incorporation of sterilizing agents in the compositions or by irradiation. They may also be manufactured in the form of sterile solid compositions, for example, by freeze-drying, which may be dissolved in sterile water or some other sterile diluent(s) for injection immediately before used.

Other compositions for parenteral administration include liquids for external use, and endermic liniments, ointment, suppositories and pessaries which comprise one or more of the active compound(s) and may be prepared by methods known *per se*.

20 Reference examples and Examples

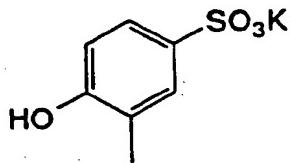
The following reference examples and examples illustrate, but do not limit, the present invention.

The solvents in parentheses show the developing or eluting solvents and the ratios of the solvents used are by volume in chromatographic separations and TLC.

The NMR data show the solvents used in the measurements in parentheses.

Reference example 1

30 3-methyl-4-hydroxybenzenesulfonic acid • potassium salt



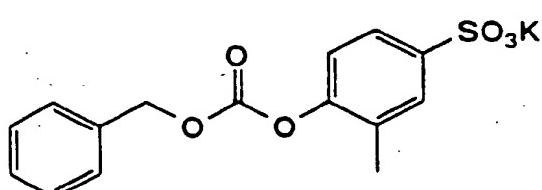
40 To stirring conc. sulfuric acid (26 ml) at 100 °C was slowly added o-cresol (50 ml), the mixture was stirred at 100 °C for 5 hours. After the reaction mixture was cooled at room temperature, to mixture was neutralized by slowly adding potassium hydroxide (27.5 g) in water (35 ml) solution. After to the mixture was added methanol (100 ml), the precipitate was filtered to give the title compound (56.5 g) having the following physical data.

TLC : Rf 0.18 (chloroform:methanol:water=6:4:1).

45 Reference example 2

3-methyl-4-(benzyloxycarbonyloxy)benzenesulfonic acid • potassium salt

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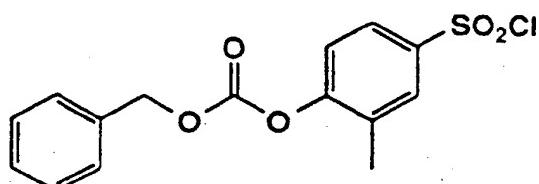
EP 0 769 498 A1

To a suspension of the compound prepared in reference example 1 (12.2 g) in tetrahydrofuran (THF) (100 ml) was added 2N aqueous solution of sodium hydroxide (28 ml) at room temperature, following added benzylloxycarbonyl chloride (8 ml) under cooling with ice. The reaction mixture was stirred for 30 min. The reaction mixture was concentrated under reduced pressure, and cooled with ice, and the precipitate was filtered to give the title compound (7.3 g) having the following physical data.

TLC : Rf 0.51 (chloroform:methanol:water=6:4:1)

Reference example 3

10 3-methyl-4-(benzyloxycarbonyloxy)benzenesulfonyl chloride



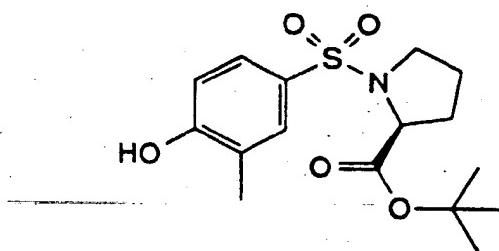
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To a suspension of the compound prepared in reference example 2 (46.1 g) in dimethylformamide (DMF) (100 ml) was slowly added thionyl chloride (15 ml) under cooling with ice. The reaction mixture was stirred for 30 min at 5 °C. To the reaction mixture was added ice water, and the precipitate was filtered to give the title compound (39.4 g) having the following physical data.

TLC : Rf 0.56 (chloroform:methanol:water=6:4:1)

Reference example 4

30 4-(2S-t-butyloxycarbonylpyrrolidin-1-ylsulfonyl)-2-methylphenol



To a solution of L-proline-t-butylester (1.9 g) in pyridine (10 ml) was added the compound prepared in reference example 3 (3.7 g) under cooling with ice. The reaction mixture was stirred for 30 min. The mixture was quenched by adding 2N aqueous solution hydrochloric acid and extracted with ethyl acetate (200 ml). The organic layer was washed with a saturated aqueous solution of sodium hydrocarbonate and a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. 10 % Palladium on activated carbon (500 mg) was added to a solution of the residue (4.9 g) in methanol (200 ml) and the mixture was stirred for 2 h at room temperature under an atmosphere of hydrogen. The mixture was filtered through Celite (being on sale). The filtrate was concentrated to give the title compound (3.4 g) having the following physical data.

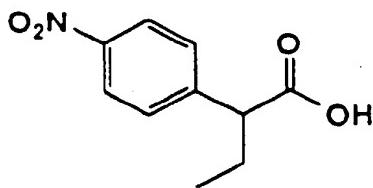
TLC : Rf 0.35 (hexane:ethyl acetate=1:1).

Reference example 5

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2RS-(4-nitrophenyl)butanoic acid

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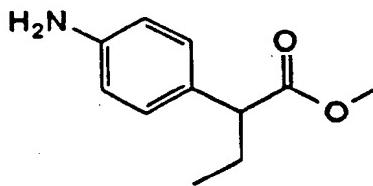
To a mixture solution of 2-phenylbutanoic acid (200 g) in acetic acid (200 ml) and conc. sulfuric acid (150 ml) was slowly added conc. nitric acid (150 ml) at 15 °C. The reaction mixture was stirred for 10 min at same temperature. The reaction mixture was poured into ice water, and the precipitate was filtered. The residue was recrystallized from the mixture solution of hexane/ethyl acetate to give the title compound (103 g) having the following physical data.

15 TLC : Rf 0.50 (ethyl acetate).

Reference example 6

20 2RS-(4-aminophenyl)butanoic acid methylester

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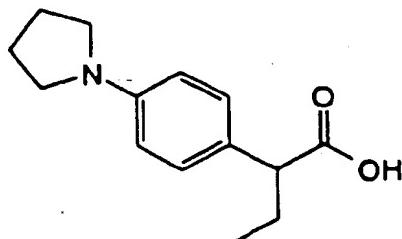
To a solution of the compound prepared in reference example 5 (15.7 g) in DMF (60 ml) was added potassium carbonate (12 g) under cooling with ice. To the mixture was added methyl iodide (5 ml) at same temperature. The reaction mixture was stirred for 2h at room temperature. The mixture was quenched by adding 1N aqueous solution hydrochloric acid (200 ml) and extracted with the mixture of hexane/ethyl acetate (1:1, 200 ml). The organic layer was washed with water and a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. 5 % Palladium on activated carbon (1.3 g) was added to a solution of the residue in methanol (300 ml) and the mixture was stirred for 2 h at room temperature under an atmosphere of hydrogen. The mixture was filtered through Celite (being on sale). The filtrate was concentrated to give the title compound (14.2 g) having the following physical data.

40 TLC : Rf 0.47 (hexane:ethyl acetate=1:1).

Reference example 7

45 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid

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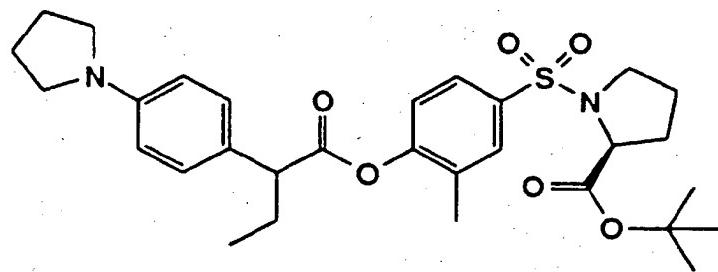
To a solution of the compound prepared in reference example 6 (14.2 g) in DMSO (75 ml) was added potassium carbonate (11 g) and 1,4-dibromobutane (9 ml). The reaction mixture was stirred for 1h at 40°C. To the mixture was

added sodium iodide (11.2 g), the reaction mixture was stirred for 3h at 40 °C and stirred for 2h at 60 °C. The reaction mixture was quenched by adding water and extracted with the mixture of hexane/ethyl acetate (1:1, 1000 ml). The organic layer was washed with water and a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. To a solution of the residue in methanol (80 ml) was added 5N aqueous solution of sodium hydroxide (20 ml) and the mixture was stirred for 5 h at room temperature. To the mixture was added aqueous solution hydrochloric acid until pH 8, and washed with ethyl acetate. The water layer was neutralized by adding aqueous solution hydrochloric acid, and extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was recrystallized from the mixture solution of hexane/ethyl acetate (3:1) to give the title compound (9.83 g) having the following physical data.

TLC : Rf 0.30 (hexane:ethyl acetate=1:1).

Example 1

4-(2S-t-butyloxycarbonylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



To a solution of the compound prepared in reference example 4 (748 mg), the compound prepared in reference example 7 (537 mg) and dimethylaminopyridine (64 mg) in dichloromethane (20 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (482 mg) at room temperature. The reaction mixture was stirred for 2h at room temperature. To the reaction mixture was added ethyl acetate, and washed with 1N aqueous solution hydrochloric acid (x2). The organic layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 5 : 1) to give the title compound (1.04 g) having the following physical data.

TLC : Rf 0.23 (hexane:ethyl acetate=5:1).

Example 1(1)~1(147)

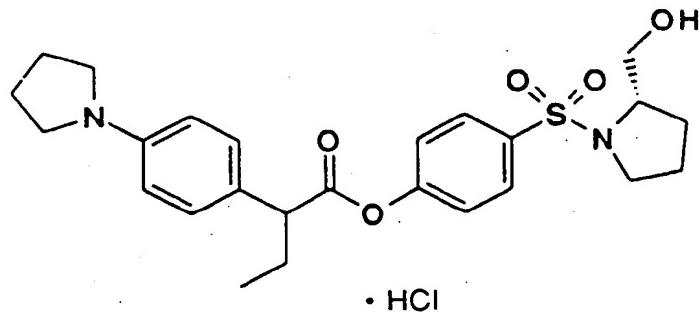
By the same procedure as example 1 and by known method converted to corresponding salts or acid addition salts, the compounds having the following physical data were given by using corresponding phenol derivatives instead of the compound prepared in reference example 4 and by using corresponding carboxylic acid derivatives instead of the compound prepared in reference example 7.

Example 1(1)

4-(2S-hydroxymethylpyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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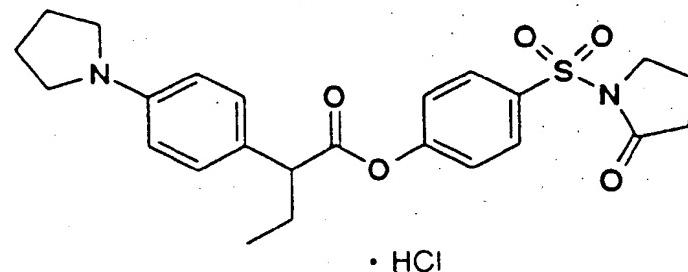
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15 NMR (DMSO-d₆): δ 7.85 (2H, d, J=9Hz), 7.28 (2H, d, J=9Hz), 7.28 (2H, d, J=9Hz), 6.83 (2H, d, J=9Hz), 3.75 (1H, t, J=7Hz), 3.60-3.44 (2H, m), 3.40-3.20 (6H, m), 3.11-2.95 (1H, m), 2.21-1.90 (5H, m), 1.90-1.65 (3H, m), 1.55-1.30 (2H, m), 0.90 (3H, t, J=7Hz);
TLC : Rf 0.48 (ethyl acetate:hexane=1:1).

Example 1(2)

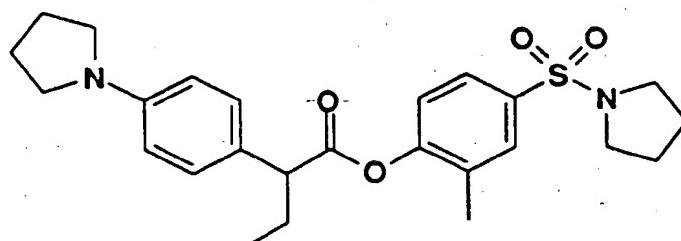
20 4-(2-oxopyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl) butanoic acid ester · hydrochloride



35 NMR(CDCl₃): δ 8.05 (2H, d, J=8.8Hz), 7.61 (2H, d, J=8.6Hz), 7.47 (2H, d, J=8.6Hz), 7.19 (2H, d, J=8.8Hz), 3.89 (2H, t, J=7.2Hz), 3.74 (1H, t, J=7.8Hz), 3.85-3.45 (4H, brs), 2.44 (2H, t, J=7.8Hz), 2.40-2.25 (4H, m), 2.35-1.75 (2H, m), 2.20-2.00 (2H, m), 0.99 (3H, t, J=7.4Hz);
TLC : Rf 0.39 (ethyl acetate:hexane=1:1).

Example 1(3)

40 4-(pyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl) phenyl)butanoic acid ester



55 NMR (CDCl₃): δ 7.68-7.57 (2H, m), 7.23 (2H, d, J=8Hz), 7.06 (1H, d, J=8Hz), 6.55 (2H, d, J=8Hz), 3.61 (1H, t, J=7Hz), 3.35-3.13 (8H, m), 2.30-1.65 (13H, m), 0.98 (3H, t, J=7Hz);
TLC : Rf 0.49 (ethyl acetate:hexane=3:7).

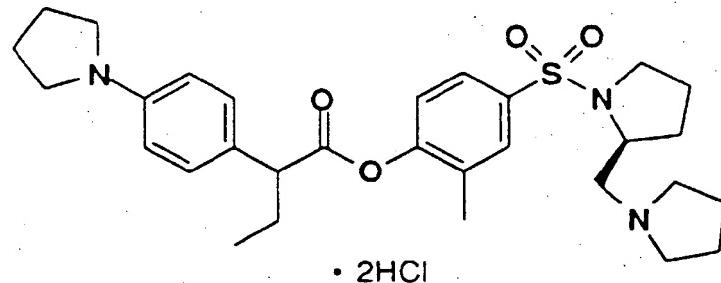
Example 1(4)

4-(2S-(pyrrolidin-1-ylmethyl)pyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

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NMR (CD_3OD): 87.95-7.75 (2H, m), 7.65 (4H, s), 7.22 (1H, d, $J=8.5\text{Hz}$), 4.26-3.90 (2H, m), 3.99 (1H, t, $J=7.5\text{Hz}$),
3.90-3.70 (5H, m), 3.50-3.10 (6H, m), 2.40-2.25 (4H, m), 2.40-1.35 (10H, m), 2.07 (3H, s), 1.00 (3H, t, $J=7.5\text{Hz}$);
TLC : Rf 0.43 (water:methanol:chloroform=1:10:90).

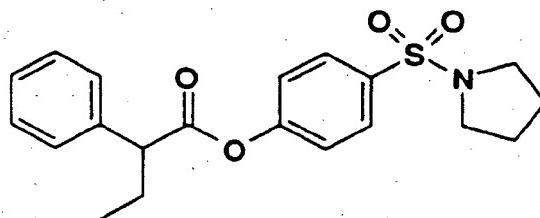
Example 1(5)

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4-(pyrrolidin-1-ylsulfonyl)phenyl 2RS-phenylbutanoic acid ester

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NMR (CDCl_3): 87.85-7.74 (2H, m), 7.41-7.24 (5H, m), 7.23-7.10 (2H, m), 3.71 (1H, t, $J=7\text{Hz}$), 3.30-3.15 (4H, m),
2.39-2.10 (1H, m), 2.03-1.80 (1H, m), 1.80-1.68 (4H, m), 0.99 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.43 (hexane:ethyl acetate=2:1).

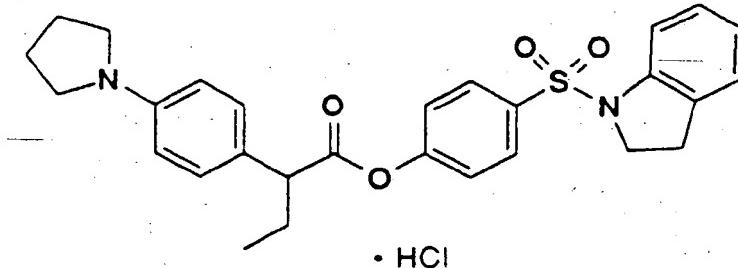
Example 1(6)

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4-(indolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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EP 0 769 498 A1

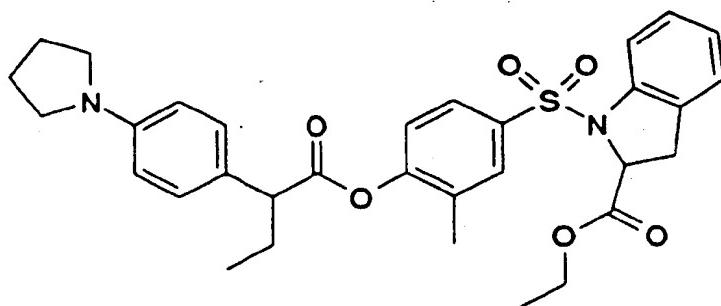
NMR (CDCl_3): δ 7.78 (2H, d, $J=8.8\text{Hz}$), 7.62 (1H, d, $J=8.0\text{Hz}$), 7.50-7.34 (4H, m), 7.24-7.12 (1H, m), 7.08 (3H, d, $J=8.8\text{Hz}$), 6.97 (1H, dt, $J=1.0$ and 7.2Hz), 3.90 (2H, d, $J=8.4\text{Hz}$), 3.68 (1H, t, $J=7.6\text{Hz}$), 3.70-3.45 (4H, m), 2.89 (2H, t, $J=8.4\text{Hz}$), 2.40-2.20 (4H, m), 2.30-2.05 and 2.00-1.75 (each 1H, m), 0.96 (3H, t, $J=7.2\text{Hz}$);
 TLC : Rf 0.47 (ethyl acetate:hexane=1:2).

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Example 1(7)

4-(2-(ethoxycarbonyl)indolin-1-ylsulfonyl)2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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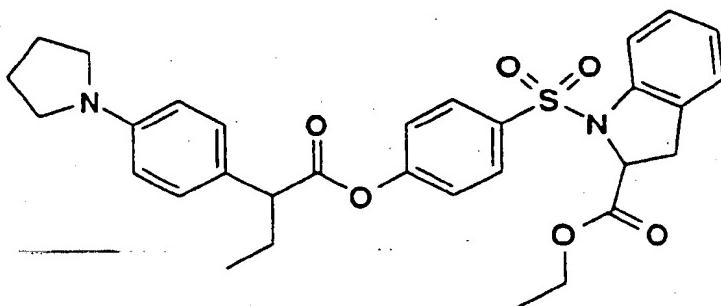
25

NMR (CDCl_3): 87.7-7.5 (m, 3H), 7.2-6.9 (m, 6H), 6.8-6.4 (m, 2H), 4.71 (q, $J=5.2\text{Hz}$, 1H), 4.23 (q, $J=7.2\text{Hz}$, 2H), 3.57 (t, $J=7.6\text{Hz}$, 1H), 3.4-3.0 (m, 6H), 2.4-1.8 (m, 9H), 1.29 (t, $J=7.2\text{Hz}$, 3H), 1.0-0.9 (m, 3H);
 TLC : Rf 0.63 (hexane:ethyl acetate=2:1).

Example 1(8)

4-(2-(ethoxycarbonyl)indolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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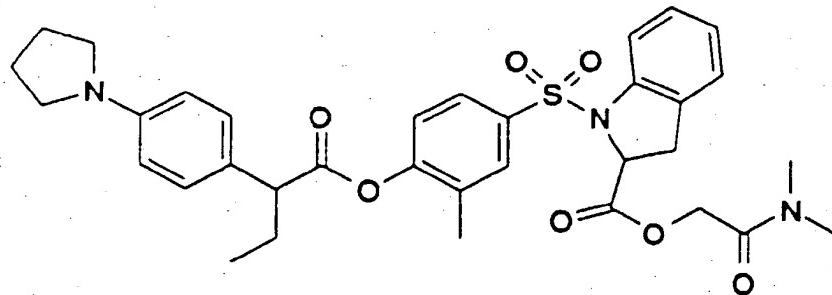
45

NMR (CDCl_3): 87.77 (2H, d, $J=8.5\text{Hz}$), 7.53 (1H, d, $J=8.0\text{Hz}$), 7.24-6.93 (7H, m), 6.52 (2H, d, $J=8.5\text{Hz}$), 4.71 (1H, dd, $J=10.0, 5.5\text{Hz}$), 4.24 (2H, q, $J=7.0\text{Hz}$), 3.54 (1H, t, $J=8.0\text{Hz}$), 3.32-3.22 (4H, m), 3.22 (1H, dd, $J=10.0, 16.0\text{Hz}$), 3.06 (1H, dd, $J=16.0, 5.5\text{Hz}$), 2.05-1.90 (4H, m), 2.25-1.70 (2H, m), 1.29 (3H, t, $J=7.0\text{Hz}$), 0.95 (3H, t, $J=7.5\text{Hz}$);
 TLC : Rf 0.57 (hexane:ethyl acetate=1:1).

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Example 1(9)
 4-(2RS-(N,N-dimethylaminocarbonylmethoxycarbonyl)indolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

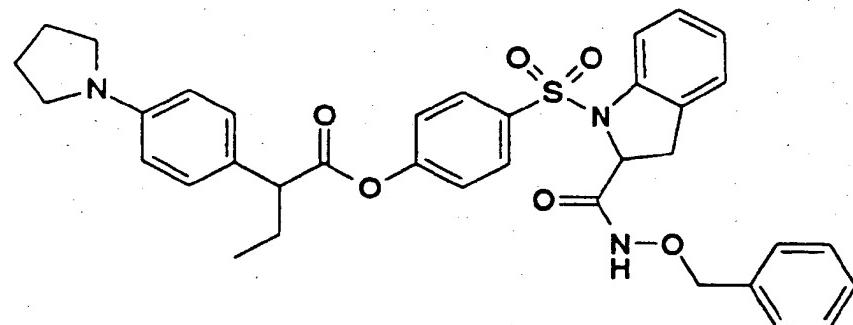
55



15 NMR (CDCl_3): δ 7.7-7.5 (m, 3H), 7.2-6.9 (m, 6H), 6.54 (d, $J=8.6\text{Hz}$, 2H), 4.85 (d, $J=14.5\text{Hz}$, 1H), 4.82 (dd, $J=1.0$, 10.8Hz, 1H), 4.70 (d, $J=14.5\text{Hz}$, 1H), 3.58 (t, $J=7.7\text{Hz}$, 1H), 3.65-3.50 (m, 1H), 3.45 (dd, $J=10.8$, 16.1Hz, 1H), 3.4-3.2 (m, 4H), 2.96 (s, 3H), 2.94 (s, 3H), 2.3-1.8 (m, 6H), 1.97 (s, 3H), 0.96 (t, $J=7.4\text{Hz}$, 3H);
TLC : Rf 0.52 (chloroform:ethyl acetate=1:1).

20 Example 1(10)

4-(2RS-(N-benzyloxycarbamoyl)indolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



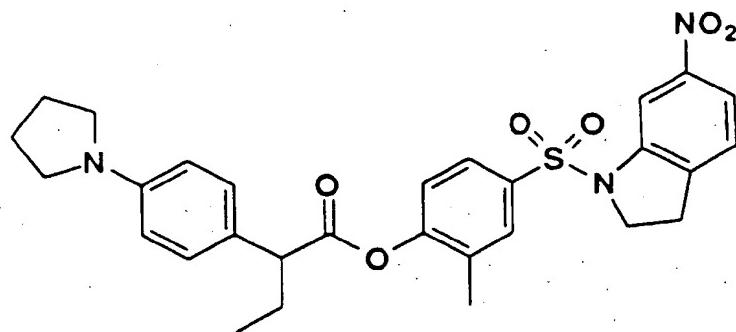
40 NMR (CDCl_3): δ 9.22 (1H, s), 7.60 (1H, d, $J=8.0\text{Hz}$), 7.51 (2H, d, $J=9.0\text{Hz}$), 7.29 (5H, s), 7.17-7.00 (8H, m), 6.52 (2H, d, $J=9.0\text{Hz}$), 4.88 (2H, s), 4.60 (1H, dd, $J=10.0\text{Hz}$, 1.5Hz), 3.53 (1H, t, $J=7.0\text{Hz}$), 3.26 (5H, t-like, $J=6.0\text{Hz}$), 2.74 (1H, dd, $J=16.0\text{Hz}$, 10.0Hz), 2.20-1.77 (2H, m), 2.03-1.98 (4H, m), 0.92 (3H, t, $J=7.0\text{Hz}$);
TLC : Rf 0.44 (hexane:ethyl acetate=1:1).

45 Example 1(11)

4-(6-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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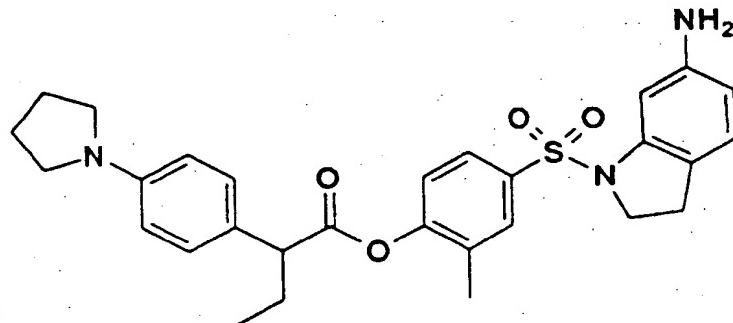
55



15 NMR (CDCl_3): δ 8.10 (dd, $J=2.4, 8.8\text{Hz}$, 1H), 7.96 (s, 1H), 7.7-7.6 (m, 3H), 7.18 (d, $J=8.4\text{Hz}$, 2H), 7.05 (d, $J=8.0\text{Hz}$, 1H) 6.52 (d, $J=8.4\text{Hz}$, 2H), 4.01 (t, $J=8.6\text{Hz}$, 2H), 3.58 (t, $J=7.8\text{Hz}$, 1H), 3.3-3.2 (m, 4H), 3.08 (t, $J=8.6\text{Hz}$, 2H), 2.3-1.8 (m, 2H), 2.00 (s, 3H), 2.1-1.9 (m, 4H), 0.96 (t, $J=7.4\text{Hz}$, 3H);
TLC : Rf 0.33 (hexane:ethyl acetate=3:1).

20 Example 1(12)

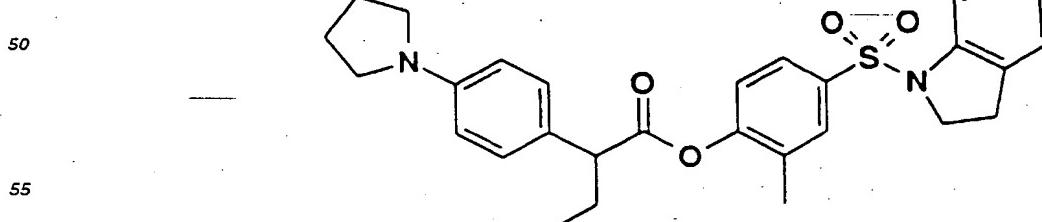
4-(6-aminoindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



40 NMR (CDCl_3): δ 7.6-7.4 (m, 3H), 7.20 (d, $J=8.7\text{Hz}$, 2H), 6.94 (d, $J=8.4\text{Hz}$, 1H), 6.53 (d, $J=8.7\text{Hz}$, 2H), 6.6-6.4 (m, 2H), 3.83 (t, $J=8.2\text{Hz}$, 2H), 3.58 (t, $J=7.7\text{Hz}$, 1H), 3.4-3.2 (m, 4H), 2.64 (t, $J=8.2\text{Hz}$, 2H), 2.3-1.8 (m, 6H), 1.95 (s, 3H), 0.97 (t, $J=7.4\text{Hz}$, 3H);
TLC : Rf 0.59 (hexane:ethyl acetate=1:1).

Example 1(13)

45 4-(7-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



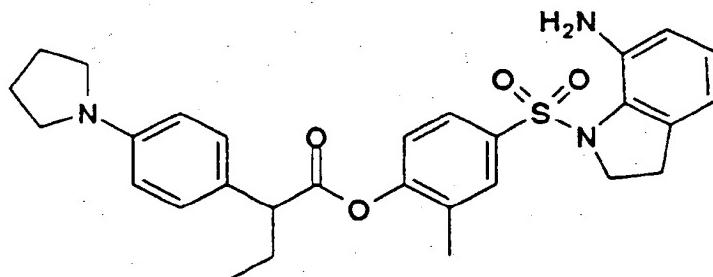
NMR (CDCl_3): δ 8.38 (d, $J=2.2\text{Hz}$, 1H), 7.85 (dd, $J=2.0$, 8.4Hz , 1H), 7.8-7.6 (m, 2H), 7.2-7.1 (m, 1H), 7.18 (d, $J=8.6\text{Hz}$, 2H), 7.03 (d, $J=8.2\text{Hz}$, 1H), 6.52 (d, $J=8.6\text{Hz}$, 2H), 3.99 (t, $J=8.6\text{Hz}$, 2H), 3.58 (t, $J=7.6\text{Hz}$, 1H), 3.3-3.2 (m, 4H), 3.05 (t, $J=8.6\text{Hz}$, 2H), 2.3-1.7 (m, 9H), 0.96 (t, $J=7.4\text{Hz}$, 3H);
TLC : Rf 0.49 (hexane:ethyl acetate=1:1).

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Example 1(14)

4-(7-aminoindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR (CDCl_3): δ 7.6-7.5 (m, 2H), 7.15 (d, $J=8.6\text{Hz}$, 2H), 7.0-6.9 (m, 2H), 6.82 (d, $J=8.0\text{Hz}$, 1H), 6.52 (d, $J=8.6\text{Hz}$, 2H), 6.29 (dd, $J=2.0$, 8.0Hz , 1H), 3.84 (t, $J=8.0\text{Hz}$, 2H), 3.58 (t, $J=7.6\text{Hz}$, 1H), 3.4-3.2 (m, 4H), 2.76 (t, $J=7.6\text{Hz}$, 2H), 2.3-1.8 (m, 9H), 0.97 (t, $J=7.4\text{Hz}$, 3H);
TLC : Rf 0.40 (hexane:ethyl acetate=2:1).

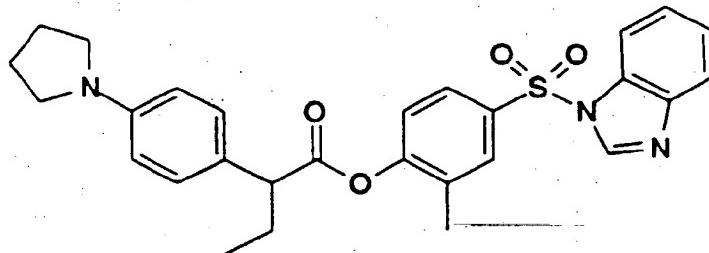
Example 1(15)

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4-(benzimidazol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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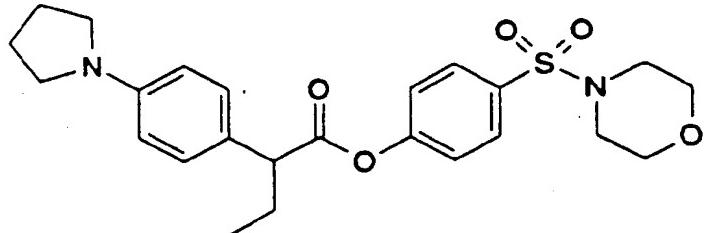
NMR (CDCl_3): δ 8.35 (1H, s), 7.79 (4H, m), 7.35 (2H, m), 7.17 (2H, d, $J=8.8\text{Hz}$), 7.08 (1H, d, $J=9.4\text{Hz}$), 6.52 (2H, d, $J=8.8\text{Hz}$), 3.57 (1H, t, $J=7.8\text{Hz}$), 3.26 (4H, m), 2.10 (1H, m), 2.00 (3H, s), 1.97 (4H, m), 1.88 (1H, m), 0.95 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.49 (hexane:ethyl acetate=2:1).

Example 1(16)

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4-(morpholin-4-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

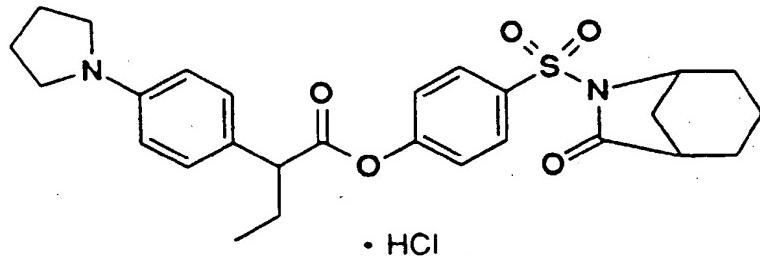
55



NMR (DMSO-d₆): δ 7.75 (2H, d, J=7Hz), 7.27 (2H, d, J=7Hz), 7.16 (2H, d, J=7Hz), 6.52 (2H, d, J=7Hz), 3.67 (1H, t, J=7Hz), 3.61 (4H, t-like), 3.20 (4H, t-like), 2.83 (4H, t-like), 2.04 (1H, m), 1.94 (4H, t-like), 1.79 (1H, m), 0.88 (3H, t, J=7Hz);
15 TLC : Rf 0.54 (hexane:ethyl acetate=1:1).

Example 1(17)

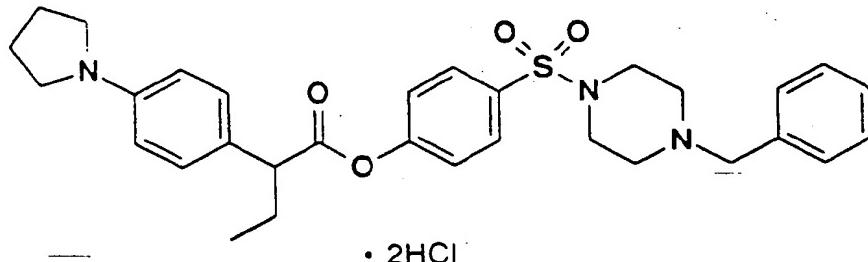
20 4-(6-aza-7-oxo-bicyclo[3.2.1]octan-6-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



35 NMR (CDCl₃): δ 8.19 (2H, d, J=9Hz), 7.38 (2H, d, J=9Hz), 7.19 (4H, d, J=9Hz), 4.65-4.55 (1H, m), 3.68 (1H, t, J=7Hz), 3.61-3.37 (4H, m), 2.59-2.49 (1H, m), 2.35-1.46 (12H, m), 1.35-1.10 (2H, m), 0.99 (3H, t, J=7Hz);
TLC : Rf 0.17 (ethyl acetate:hexane=1:3).

Example 1(18)

40 4-(4-benzylpiperazin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

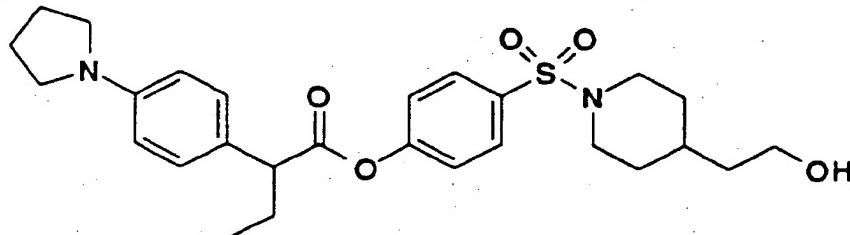


55 NMR (CD₃OD): δ 7.83 (2H, d, J=8.6Hz), 7.75-7.40 (9H, m), 7.29 (2H, d, J=8.6Hz), 4.35 (2H, s), 4.00-3.62 (7H, m), 3.60-3.40 (2H, m), 3.30-3.10 (2H, m), 2.98-2.72 (2H, m), 2.38-2.10 (5H, m), 2.04-1.80 (1H, m), 0.99 (3H, t, J=7.4Hz);
TLC:Rf 0.40 (ethyl acetate:hexane=3:7).

Example 1(19)

4-(4-(2-hydroxyethyl)piperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR (CDCl_3): δ 7.71 (2H, d, $J=9.0\text{Hz}$), 7.72 (2H, d, $J=8.7\text{Hz}$), 7.15 (2H, d, $J=9.0\text{Hz}$), 6.55 (2H, d, $J=8.7\text{Hz}$), 3.74 (2H, d, $J=10.2\text{Hz}$), 3.63 (2H, t, $J=6.0\text{Hz}$), 3.58 (1H, t, $J=8.0\text{Hz}$), 3.36-3.22 (4H, m), 2.35-1.78 (8H, m), 1.72 (2H, d, $J=10.0\text{Hz}$), 1.54-1.20 (5H, m), 0.98 (3H, t, $J=7.4\text{Hz}$);

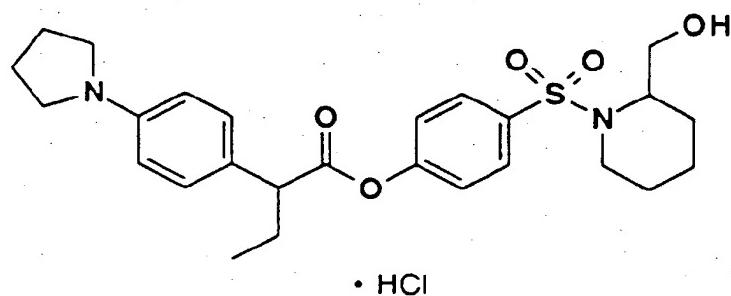
TLC : Rf 0.52 (chloroform:methanol=19:1).

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Example 1(20)

4-(2RS-hydroxymethylpiperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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NMR (DMSO-d_6): δ 7.85 (2H, d, $J=9\text{Hz}$), 7.27 (2H, d, $J=9\text{Hz}$), 7.22 (2H, d, $J=9\text{Hz}$), 6.83 (2H, d, $J=9\text{Hz}$), 3.93-3.80 (1H, m), 3.75 (1H, t, $J=7\text{Hz}$), 3.69-3.45 (2H, m), 3.45-3.20 (5H, m), 3.06-2.88 (1H, m), 2.21-1.80 (5H, m), 1.80-1.64 (2H, m), 1.55-1.30 (3H, m), 1.30-0.99 (2H, m), 0.90 (3H, t, $J=7\text{Hz}$);

TLC : Rf 0.46 (ethyl acetate:hexane=1:1).

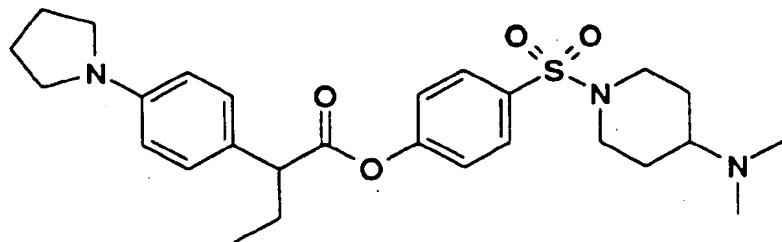
40

Example 1(21)

4-(4-(N,N-dimethylamino)piperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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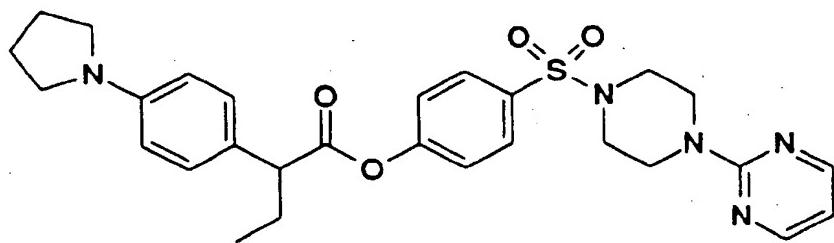
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NMR (CDCl_3): δ 7.71 (2H, d, $J=8.7\text{Hz}$), 7.20 (2H, d, $J=8.8\text{Hz}$), 7.16 (2H, d, $J=8.7\text{Hz}$), 6.54 (2H, d, $J=8.8\text{Hz}$), 3.75 (2H, d, $J=13.7\text{Hz}$), 3.58 (1H, t, $J=7.7\text{Hz}$), 3.29 (4H, t, $J=6.6\text{Hz}$), 2.36-1.53 (19H, m), 0.98 (3H, t, $J=7.4\text{Hz}$);
15 TLC : Rf 0.25 (hexane:ethyl acetate=2:1).

Example 1(22)

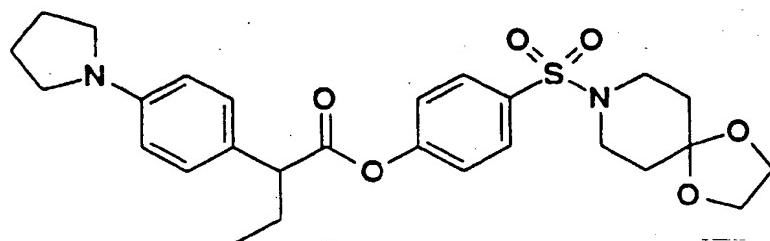
20 4-(4-(pyrimidin-2-yl)piperazin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



NMR (CDCl_3): δ 8.26 (2H, d, $J=8.8\text{Hz}$), 7.72 (2H, d, $J=8.7\text{Hz}$), 7.22-7.12 (4H, m), 6.56-6.47 (3H, m), 3.93 (4H, t, $J=5.2\text{Hz}$), 3.57 (1H, t, $J=7.7\text{Hz}$), 3.31-3.25 (4H, m), 3.04 (4H, t, $J=5.1\text{Hz}$), 2.25-1.65 (6H, m), 0.97 (3H, t, $J=7.3\text{Hz}$);
35 TLC : Rf 0.43 (hexane:ethyl acetate=1:1).

Example 1(23)

40 4-(1,4-dioxa-8-azaspiro[4.5]decan-8-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

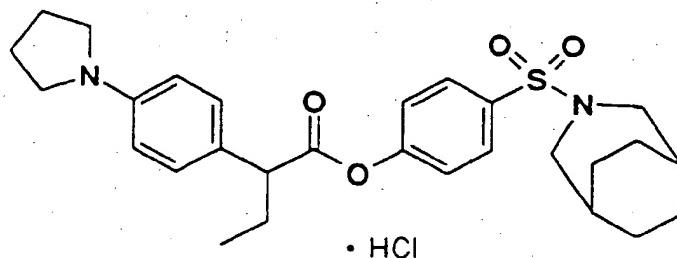


NMR (CDCl_3): δ 7.72 (2H, d, $J=8.7\text{Hz}$), 7.24-7.15 (4H, m), 6.56 (2H, d, $J=8.7\text{Hz}$), 3.89 (4H, s), 3.59 (1H, t, $J=7.7\text{Hz}$), 3.29 (4H, t, $J=6.6\text{Hz}$), 3.14 (4H, t, $J=5.7\text{Hz}$), 2.30-1.61 (10H, m), 0.98 (3H, t, $J=7.4\text{Hz}$);
55 TLC : Rf 0.48 (hexane:ethyl acetate=1:1).

Example 1(24)

4-(3-azabicyclo[3.2.2]nonan-3-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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15 NMR (CDCl₃): δ 7.73 (2H, d, J=8.6Hz), 7.53 (2H, d, J=8.6Hz), 7.45 (2H, d, J=8.6Hz), 7.15 (2H, d, J=8.8Hz), 3.72 (1H, t, J=7.6Hz), 3.75-3.50 (4H, m), 3.22 (4H, d, J=4.2Hz), 2.40-2.20 (4H, m), 2.40-1.75 (2H, m), 2.10-2.00 (2H, m), 1.80-1.50 (8H, m), 0.99 (3H, t, J=7.4Hz);
 TLC : Rf 0.57 (ethyl acetate:hexane=1:3).

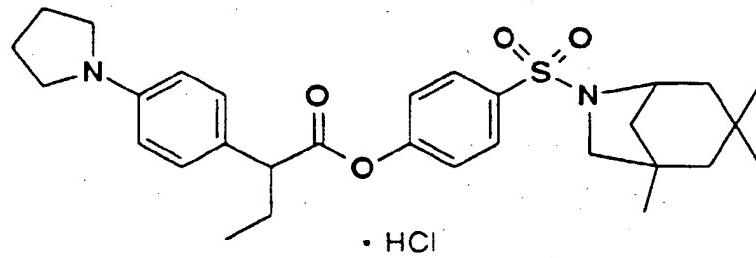
Example 1(25)

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4-(1,3,3-trimethyl-6-azabicyclo[3.2.1]octan-6-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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NMR (CDCl₃): δ 7.81 (2H, d, J=8.8Hz), 7.40 (2H, d, J=8.4Hz), 7.36-7.18 (2H, brs), 7.15 (2H, d, J=8.8Hz), 4.08 (1H, t-like), 3.69 (1H, t, J=7.8Hz), 3.64-3.38 (4H, m), 3.32 (1H, d, J=9.6Hz), 2.76 (1H, dd, J=9.6 and 1.4Hz), 2.36-2.08 (5H, m), 2.02-1.76 (2H, m), 1.52 (2H, d, J=14.4Hz), 1.34 (2H, d, J=12.4Hz), 1.22 (3H, s), 1.16-1.02 (1H, m), 0.99 (3H, t, J=7.4Hz), 0.94 (3H, s), 0.92 (3H, s);
 TLC : Rf 0.54 (ethyl acetate:hexane=1:3).

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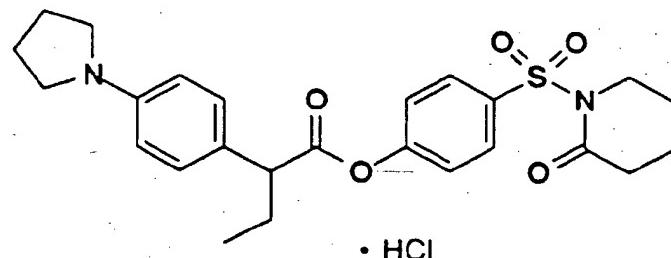
Example 1(26)

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4-(2-oxopiperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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NMR (CDCl₃): δ 8.03 (2H, d, J=9.0Hz), 7.65 (2H, d, J=8.6Hz), 7.48 (2H, d, J=8.6Hz), 7.17 (2H, d, J=9.0Hz), 3.89

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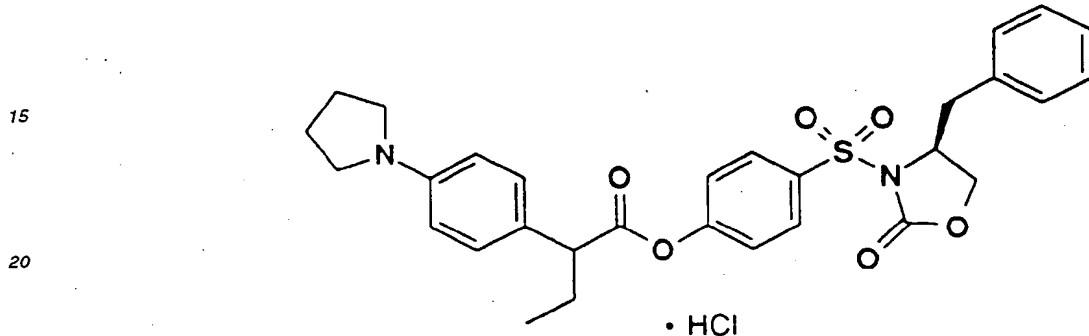
(2H, t, J=5.8Hz), 3.74 (1H, t, J=7.8Hz), 3.80-3.50 (4H, m), 2.42 (2H, t, J=6.6Hz), 2.50-2.25 (4H, m), 2.40-1.70 (2H, m), 2.00-1.70 (4H, m), 0.99 (3H, t, J=7.4Hz);

TLC : Rf 0.83 (acetic acid:methanol:chloroform=1:2:40).

5 Example 1(27)

4-(2-oxo-4S-benzyltetrahydroxazol-3-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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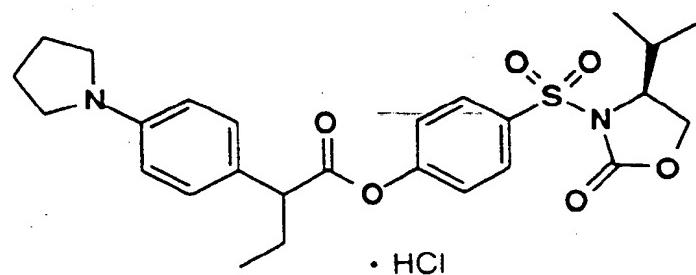


NMR (CDCl₃): δ 8.13 (2H, d, J=8.8Hz), 7.64 (2H, d, J=8.8Hz), 7.48 (2H, d, J=8.8Hz), 7.23 (2H, d, J=8.8Hz), 7.40-7.16 (5H, m), 4.75-4.58 (1H, m), 4.24-4.05 (2H, m), 3.76 (1H, t, J=7.6Hz), 3.85-3.50 (4H, brs), 3.50 (1H, dd, J=13.2, 3.8Hz), 2.83 (1H, dd, J=13.2, 10.2Hz), 2.44-2.26 (4H, m), 2.34-2.10 and 2.10-1.76 (each 1H, m), 0.99 (3H, t, J=7.4Hz);

TLC : Rf 0.51 (ethyl acetate:hexane=1:2).

Example 1(28)

4-(2-oxo-4S-isopropylperhydroxazol-3-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

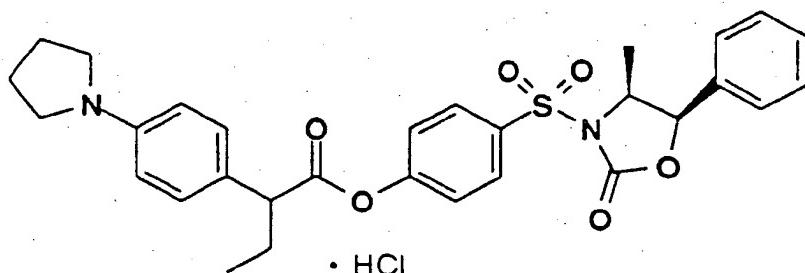


NMR(CDCl₃): δ 8.10 (2H, d, J=9.0Hz), 7.63 (2H, d, J=8.6Hz), 7.48 (2H, d, J=8.6Hz), 7.22 (2H, d, J=9.0Hz), 4.43 (1H, dt, J=8.2, 3.0Hz), 4.29 (1H, t, J=8.8Hz), 4.16 (1H, dd, J=8.8, 3.0Hz), 3.75 (1H, t, J=7.6Hz), 3.90-3.45 (4H, brs), 2.56-1.76 (7H, m), 0.99 (3H, t, J=7.2Hz), 0.93 (3H, d, J=6.8Hz), 0.75 (3H, d, J=6.8Hz);

TLC : Rf 0.62 (ethyl acetate:hexane=1:1).

Example 1(29)

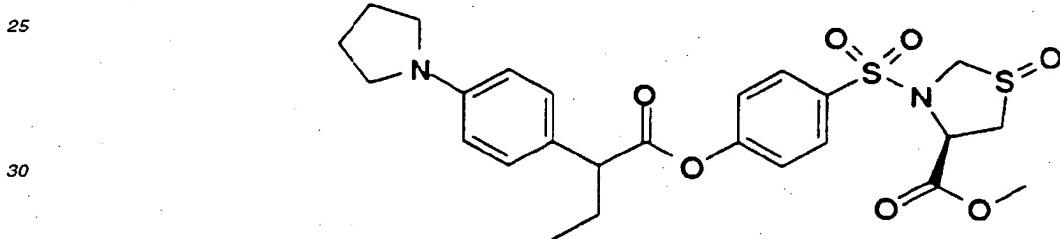
4-(2-oxo-4S-methyl-5S-phenylperhydroxazol-3-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



15 NMR (CDCl_3): δ 8.13 (2H, d, $J=8.8\text{Hz}$), 7.72 (2H, d, $J=8.8\text{Hz}$), 7.51 (2H, d, $J=8.8\text{Hz}$), 7.46-7.34 (3H, m), 7.23 (2H, d, $J=8.8\text{Hz}$), 7.30-7.20 (2H, m), 5.71 (1H, d, $J=7.2\text{Hz}$), 4.78 (1H, dq, $J=7.2\text{Hz}$), 3.77 (1H, t, $J=7.2\text{Hz}$), 3.90-3.50 (4H, brs), 2.50-2.25 (4H, brs), 2.40-1.80 (2H, m), 1.00 (3H, t, $J=7.2\text{Hz}$), 0.97 (3H, d, $J=7.2\text{Hz}$);
TLC : Rf 0.66 (ethyl acetate:hexane=1:2).

Example 1(30)

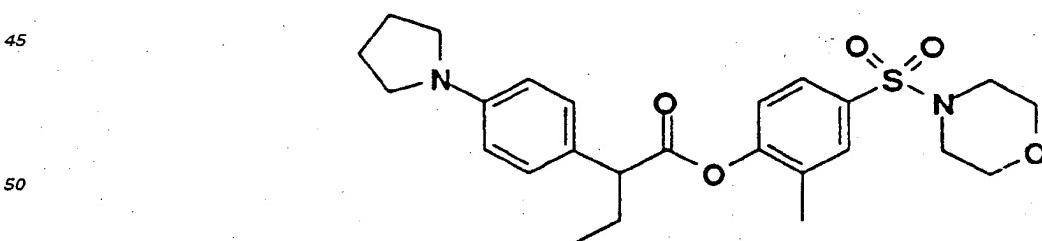
20 4-(1RS-oxo-4S-methoxycarbonylperhydrothiazol-3-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phényl)butanoic acid ester



35 NMR (CDCl_3): δ 7.87 (2H, d, $J=9.0\text{Hz}$), 7.21 (2H, d, $J=9.0\text{Hz}$), 7.19 (2H, d, $J=9.0\text{Hz}$), 6.55 (2H, d, $J=9.0\text{Hz}$),
5.28-5.16 (2H, ml, 4.09-4.01 (1H, m), 3.69-3.44 (5H, m), 3.33-3.26 (4H, m), 3.08-2.97 (1H, m), 2.24-1.80 (6H, m), 0.98 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.50 (chloroform:methanol:acetic acid=40:2:1).

Example 1(31)

40 4-(morpholin-4-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

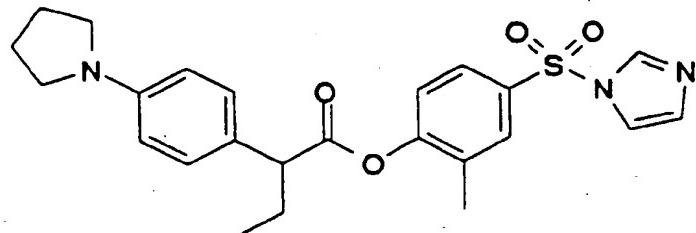


55 NMR (CDCl_3): δ 7.56-7.51 (2H, m), 7.26-7.21 (2H, m), 7.10 (1H, d, $J=8\text{Hz}$), 6.55 (2H, d, $J=8\text{Hz}$), 3.75-3.71 (4H, m), 3.62 (1H, t, $J=8\text{Hz}$), 3.32-3.26 (4H, m), 3.01-2.96 (4H, m), 2.37-1.73 (2H, m), 2.06 (3H, s), 2.04-1.96 (4H, m), 1.00 (3H, t, $J=8\text{Hz}$);
TLC : Rf 0.27 (hexane:ethyl acetate=3:1).

Example 1(32)

4-(imidazol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR (CDCl_3): 8.799 (1H, m), 7.75 (1H, s), 7.72 (1H, m), 7.27-7.08 (5H, m), 6.54 (2H, d, $J=8.8\text{Hz}$), 3.60 (1H, t, $J=7.6\text{Hz}$), 3.28 (4H, m), 2.14 (1H, m), 2.04 (3H, s), 2.01 (4H, m), 1.91 (1H, m), 0.97 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.36 (hexane:ethyl acetate=2:1).

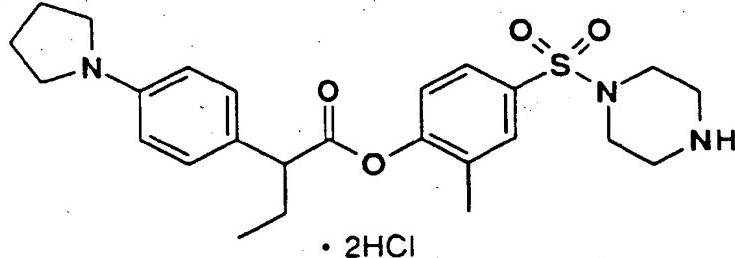
20 Example 1(33)

4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

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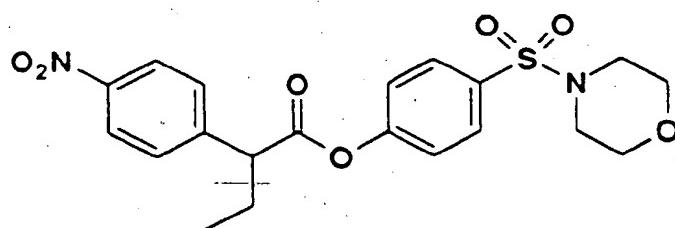
Example 1(34)

4-(morpholin-4-ylsulfonyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester

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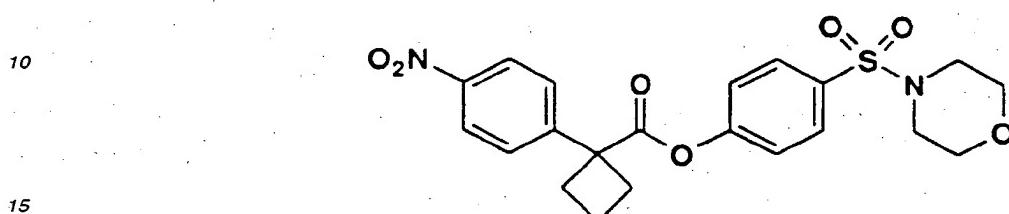


NMR (CDCl_3): 8.26 (2H, d, $J=8\text{Hz}$), 7.77 (2H, d, $J=8\text{Hz}$), 7.59 (2H, d, $J=8\text{Hz}$), 7.20 (2H, d, $J=8\text{Hz}$), 3.86 (1H, t, $J=7\text{Hz}$), 3.80-3.68 (4H, m), 3.06-2.94 (4H, m), 2.30 (1H, ddq, $J=14\text{Hz}, 7\text{Hz}, 7\text{Hz}$), 1.97 (1H, ddq, $J=14\text{Hz}, 7\text{Hz}, 7\text{Hz}$), 1.03 (3H, t, $J=7\text{Hz}$);

TLC : Rf 0.16 (hexane:ethyl acetate=7:3).

Example 1(35)

5 4-(morpholin-4-ylsulfonyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester



NMR (CDCl_3): δ 8.26 (2H, d, $J=8\text{Hz}$), 7.77 (2H, d, $J=8\text{Hz}$), 7.56 (2H, d, $J=8\text{Hz}$), 7.16 (2H, d, $J=8\text{Hz}$), 3.79-3.66 (4H, m), 3.15-2.91 (6H, m), 2.80-2.60 (2H, m), 2.39-1.91 (2H, m);
TLC : Rf 0.16 (hexane:ethyl acetate=7:3).

Example 1(36)

20 4-(6-aza-7-oxobicyclo[3.2.1]octan-6-ylsulfonyl)phenyl 2-(4-methoxyphenyl)-2-ethylbutanoic acid ester

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NMR (CDCl_3): δ 8.08 (2H, d, $J=8.8\text{Hz}$), 7.27 (2H, d, $J=8.8\text{Hz}$), 7.11 (2H, d, $J=8.8\text{Hz}$), 6.91 (2H, d, $J=8.8\text{Hz}$), 4.59 (1H, brt, $J=4.8\text{Hz}$), 3.82 (3H, s), 2.53 (1H, brs), 2.32-1.15 (12H, m), 0.84 (6H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.85 (acetic acid:methanol:chloroform=1:2:40).

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Example 1(37)

45 4-(morpholin-4-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester

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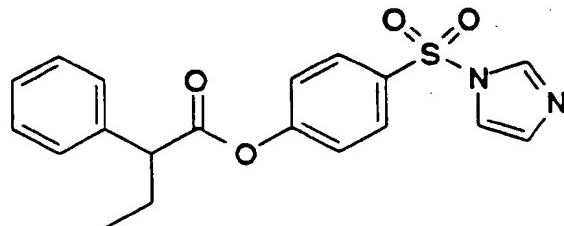
NMR (CDCl_3): δ 7.57-7.52 (2H, m), 7.30-7.08 (5H, m), 3.75-3.67 (5H, m), 3.01-2.96 (4H, m), 2.36 (3H, s), 2.32-2.13 and 2.03-1.82 (each 1H, m), 2.02 (3H, s), 1.00 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.30 (hexane:ethyl acetate=3:1).

Example 1(38)

4-(imidazol-1-ylsulfonyl)phenyl 2RS-phenylbutanoic acid ester

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NMR (CDCl_3): δ 7.99 (1H, s), 7.97-7.86 (2H, m), 7.40-7.28 (5H, m), 7.28-7.25 (1H, m), 7.25-7.15 (2H, m), 7.13-7.05 (1H, m), 3.68 (1H, t, $J=7\text{Hz}$), 2.34-2.05 (1H, m), 2.05-1.98 (1H, m), 0.96 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.29 (hexane:ethyl acetate=6:4).

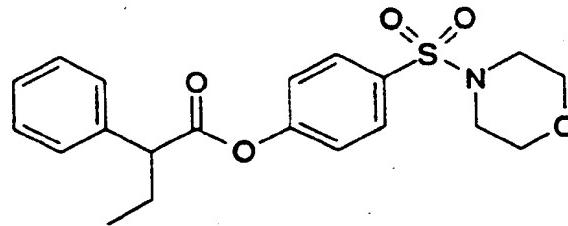
Example 1(39)

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4-(morpholin-4-ylsulfonyl)phenyl 2RS-phenylbutanoic acid ester

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NMR (CDCl_3): δ 7.78-7.67 (2H, m), 7.43-7.24 (5H, m), 7.24-7.15 (2H, m), 3.78-3.65 (5H, m), 3.03-2.93 (4H, m), 2.36-2.11 (1H, m), 2.05-1.80 (1H, m), 0.99 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.26 (hexane:ethyl acetate=2:1).

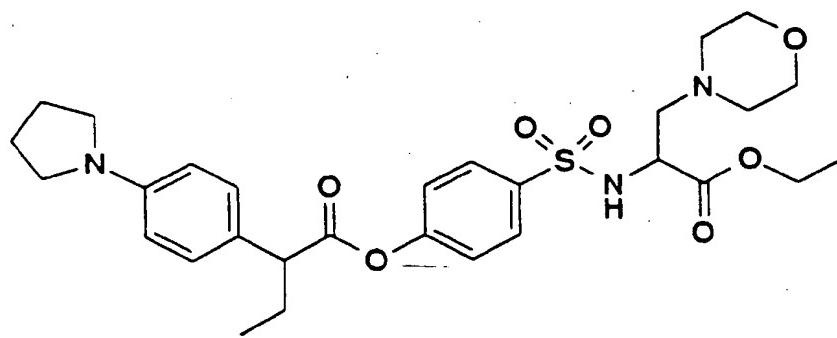
Example 1(40)

40 4-(N-1RS-(ethoxycarbonyl)-2-(morpholin-4-yl)ethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR (CDCl_3): δ 7.84 (2H, d, $J=8.6\text{Hz}$), 7.20 (2H, d, $J=8.6\text{Hz}$), 7.12 (2H, d, $J=8.6\text{Hz}$), 6.55 (2H, d, $J=8.6\text{Hz}$), 4.01 (3H, m), 3.57 (5H, m), 3.29 (4H, t, $J=6.4\text{Hz}$), 2.63 (2H, m), 2.36 (4H, m), 2.14 (1H, m), 2.01 (4H, m), 1.89 (1H, m), 1.17

(3H, t, J=7.0Hz), 0.97 (3H,t,J=7.4Hz);
 TLC : Rf 0.34 (hexane:ethyl acetate=1:1).

Example 1(41)

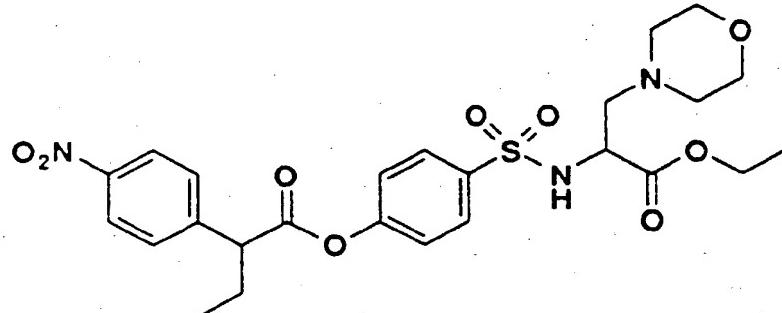
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4-(N-1RS-(ethoxycarbonyl)-2-(morpholin-4-yl)ethylsulfamoyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester

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NMR (CDCl_3): δ 8.26 (2H, d, J=8.8Hz), 7.89 (2H, d, J=8.6Hz), 7.57 (2H, d, J=8.8Hz), 7.13 (2H, d, J=8.6Hz), 4.03 (2H, q, J=7.2Hz), 3.96 (1H, t, J=7.0Hz), 3.84 (1H, t, J=7.0Hz), 3.58 (4H, m), 2.68 (1H, dd, J=13.1, 7.0Hz), 2.61 (1H, dd, J=13.1, 7.0Hz), 2.36 (4H, m), 2.82 (1H, m), 1.95 (1H, dq, J=13.6, 7.2Hz), 1.17 (3H, t, J=7.2Hz), 1.02 (3H, t, J=7.2Hz);
 TLC : Rf 0.45 (ethyl acetate).

Example 1(42)

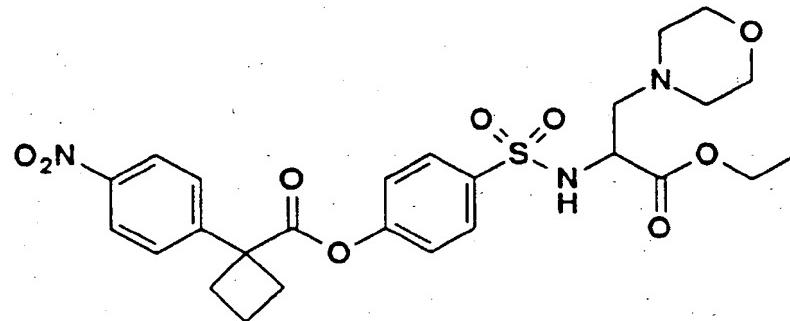
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4-(N-1RS-(ethoxycarbonyl)-2-(morpholin-4-yl)ethylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester

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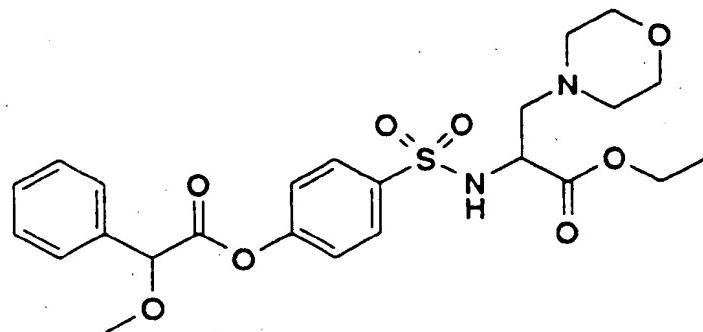
Example 1(43)

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4-(N-1RS-(ethoxycarbonyl)-2-(morpholin-4-yl)ethylsulfamoyl)phenyl 2RS-phenyl-2-methoxyacetic acid ester

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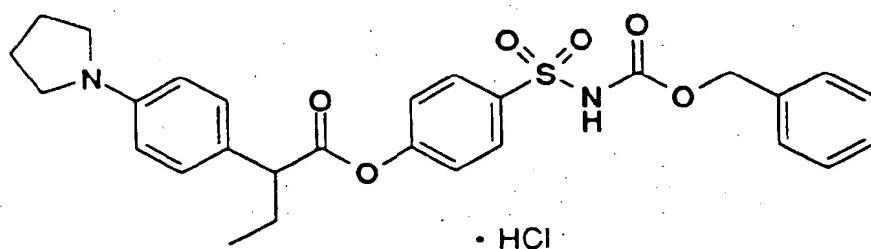
15 NMR (CDCl_3): δ 7.86 (2H, d, $J=8.8\text{Hz}$), 7.52 (2H, m), 7.42 (3H, m), 7.12 (2H, d, $J=8.8\text{Hz}$), 5.00 (1H, s), 4.01 (2H, q, $J=7.0\text{Hz}$), 3.94 (1H, t, $J=6.6\text{Hz}$), 3.57 (4H, t, $J=5.2\text{Hz}$), 3.49 (3H, s), 2.66 (1H, dd, $J=12.8, 6.6\text{Hz}$), 2.60 (1H, dd, $J=12.8, 6.6\text{Hz}$), 2.34 (4H, t, $J=5.2\text{Hz}$), 1.16 (3H, t, $J=7.0\text{Hz}$);
TLC : R_f 0.26 (hexane:ethyl acetate=1:1).

20 Example 1(44)

4-(N-benzyloxycarbonylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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NMR (CDCl_3): δ 8.3-8.0 (1H, brs), 8.00 (2H, d, $J=8.8\text{Hz}$), 7.56 (2H, d-like), 7.46 (2H, d-like), 7.38-7.22 (5H, m), 7.15 (2H, d, $J=8.8\text{Hz}$), 5.07 (2H, s), 3.74 (1H, t, $J=7.8\text{Hz}$), 3.8-3.5 (4H, m), 2.4-2.2 (4H, m), 2.40-2.10 and 2.10-1.80 (each 1H, m), 1.00 (3H, t, $J=7.2\text{Hz}$);

TLC : R_f 0.50 (acetic acid:ethyl acetate:hexane=1:8:16).

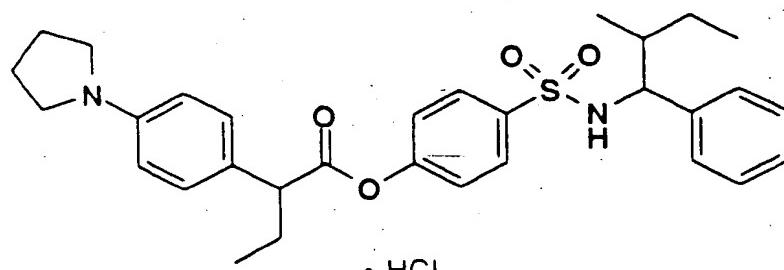
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Example 1(45)

4-(N-1RS-phenyl-2RS-methylbutylsulfamoyl)phenyl 2BS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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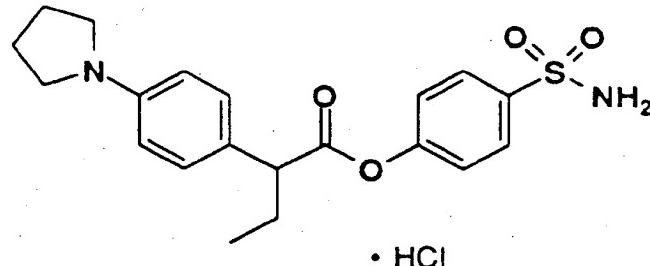


NMR (CDCl_3): δ 7.80-7.57 (2H, m), 7.57-7.32 (4H, m), 7.12-6.93 (3H, m), 6.93-6.70 (4H, m), 5.38 (1H, m), 4.19-3.99 (1H, m), 3.90-3.30 (5H, m), 2.50-2.04 (5H, m), 1.96-1.40 (3H, m), 1.28-0.57 (10H, m);
 TLC : Rf 0.24 (ethyl acetate:hexane=1:4).

5 Example 1(46)

4-sulfamoylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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NMR (CD_3OD): δ 7.88 (2H, d, $J=8.6\text{Hz}$), 7.18 (2H, d, $J=8.8\text{Hz}$), 7.11 (2H, d, $J=8.8\text{Hz}$), 6.57 (2H, d, $J=8.6\text{Hz}$), 3.61 (1H, t, $J=7.6\text{Hz}$), 3.34-3.19 (4H, m), 2.26-2.00 and 2.00-1.70 (each 1H, m), 2.07-1.96 (4H, m), 0.96 (3H, t, $J=7.4\text{Hz}$);
 TLC : Rf 0.22 (acetic acid:methanol:chloroform=1:2:40).

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Example 1(47)

4-(N-2-methoxyethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR (CDCl_3): δ 7.83 (2H, d, $J=9.0\text{Hz}$), 7.22 (2H, d, $J=8.6\text{Hz}$), 7.14 (2H, d, $J=9.0\text{Hz}$), 6.56 (2H, d, $J=8.6\text{Hz}$), 4.85 (1H, br), 3.59 (1H, t, $J=7.7\text{Hz}$), 3.42-3.20 (9H, m), 3.11 (2H, m), 2.28-1.70 (6H, m), 0.98 (3H, t, $J=7.6\text{Hz}$);
 TLC : Rf 0.55 (hexane:ethyl acetate=2:3).

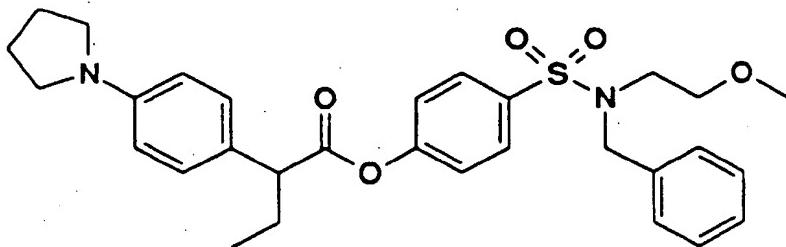
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Example 1(48)

4-(N-2-methoxyethyl-N-benzylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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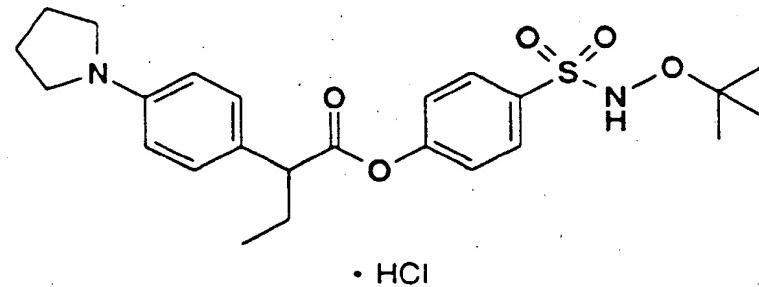
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15 NMR (CDCl_3): δ 7.82 (2H, d, $J=6.8\text{Hz}$), 7.29 (5H, s), 7.19 (2H, d, $J=8.6\text{Hz}$), 7.13 (2H, d, $J=6.8\text{Hz}$), 6.56 (2H, d, $J=8.6\text{Hz}$), 4.40 (2H, s), 3.60 (1H, t, $J=7.4\text{Hz}$), 3.2-3.4 (8H, m), 3.10 (3H, s), 1.8-2.3 (6H, m), 0.99 (3H, t, $J=7.3\text{Hz}$);
TLC : Rf 0.40 (hexane:ethyl acetate=3:1).

Example 1(49)

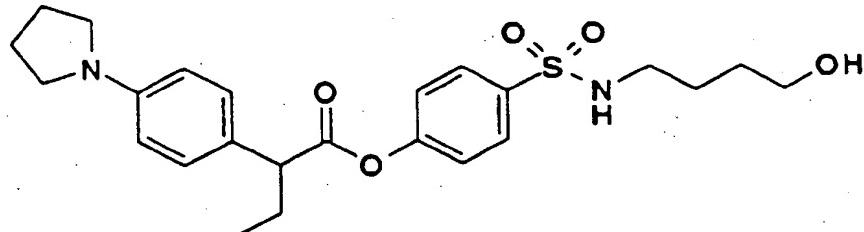
4-(N-t-butyloxysulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



NMR (CDCl_3): δ 7.88 (2H, d, $J=8.8\text{Hz}$), 7.24-7.15 (4H, m), 6.56 (2H, d, $J=8.2\text{Hz}$), 6.44 (1H, s), 3.59 (1H, t, $J=7.2\text{Hz}$), 3.33-3.26 (4H, m), 2.45-1.80 (6H, m), 1.21 (9H, s), 0.98 (3H, t, $J=7.2\text{Hz}$);
TLC : Rf 0.40 (hexane:ethyl acetate:acetic acid=5:2:0.1).

Example 1(50)

4-(N-4-hydroxybutylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



55 NMR (CDCl_3): δ 7.82 (2H, d, $J=8.7\text{Hz}$), 7.22 (2H, d, $J=8.6\text{Hz}$), 7.13 (2H, d, $J=8.7\text{Hz}$), 6.56 (2H, d, $J=8.6\text{Hz}$), 5.00 (1H, t, $J=5.2\text{Hz}$), 3.70-3.48 (3H, m), 3.40-3.12 (4H, m), 3.06-2.86 (2H, m), 2.30-1.76 (6H, m), 1.78-1.62 (1H, brs), 1.60-1.40 (4H, m), 0.97 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.48 (ethyl acetate).

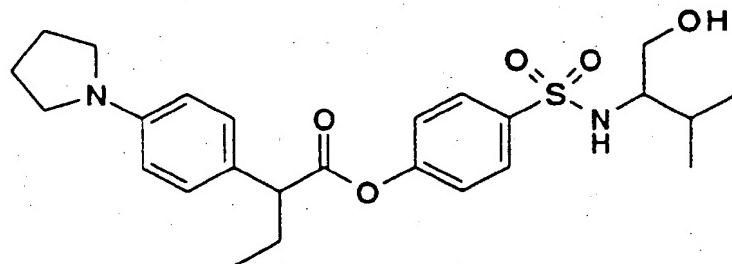
Example 1(51)

4-(N-1RS-hydroxymethyl-2-methylpropylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR (CDCl_3): δ 7.85 (2H, d, $J=8.4\text{Hz}$), 7.21 (2H, d, $J=8.6\text{Hz}$), 7.12 (2H, d, $J=8.4\text{Hz}$), 6.55 (2H, d, $J=8.6\text{Hz}$), 5.06 (1H, d, $J=8.4\text{Hz}$), 3.58 (1H, t, $J=5.8\text{Hz}$), 3.56-3.48 (2H, m), 3.36-3.22 (4H, m), 3.10-2.90 (1H, m), 2.23-1.65 (8H, m), 0.97 (3H, t, $J=7.2\text{Hz}$), 0.78 (6H, d, $J=6.8\text{Hz}$);

TLC : Rf 0.25 (ethyl acetate:hexane=2:3).

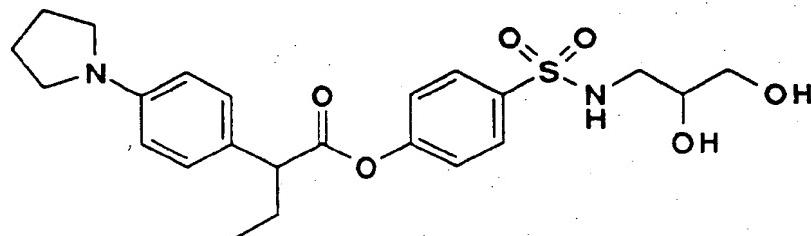
Example 1(52)

4-(N-2RS,3-dihydroxypropylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR (CDCl_3): δ 7.80 (2H, d, $J=8.6\text{Hz}$), 7.20 (2H, d, $J=8.8\text{Hz}$), 7.11 (2H, d, $J=8.6\text{Hz}$), 6.54 (2H, d, $J=8.8\text{Hz}$), 5.63 (1H, t, $J=6.3\text{Hz}$), 3.80-3.64 (1H, m), 3.62-3.41 (3H, m), 3.35-3.20 (4H, m), 3.10-2.80 (3H, m), 2.30-1.70 (7H, m), 0.96 (3H, t, $J=7.4\text{Hz}$);

TLC : Rf 0.28 (ethyl acetate:hexane=4:1).

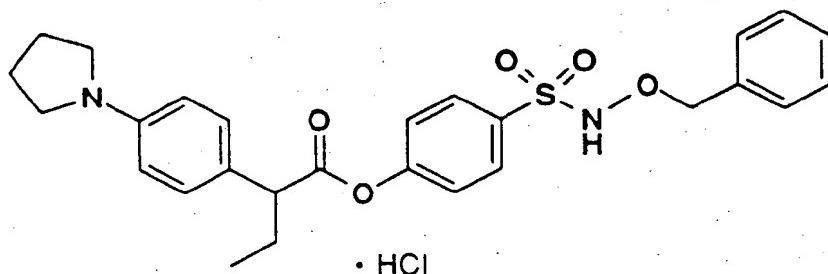
Example 1(53)

4-(N-benzyloxysulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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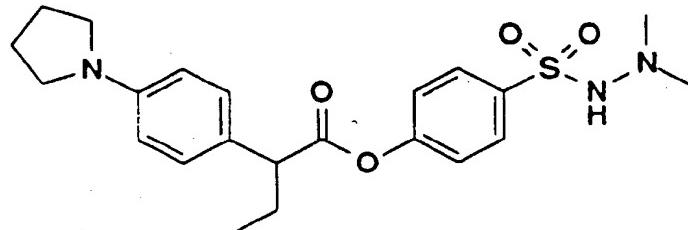
EP 0 769 498 A1

NMR (CDCl_3): δ 7.87 (2H, d, $J=8.8\text{Hz}$), 7.32-7.12 (9H, m), 6.93 (1H, s), 6.54 (2H, d, $J=8.8\text{Hz}$), 4.94 (2H, s), 3.57 (1H, t, $J=7.8\text{Hz}$), 3.31-3.25 (4H, m), 2.25-1.80 (6H, m), 0.968 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.55 (hexane:ethyl acetate:acetic acid=5:2:0.2).

5 Example 1(54)

4-(N-(N',N'-dimethylamino)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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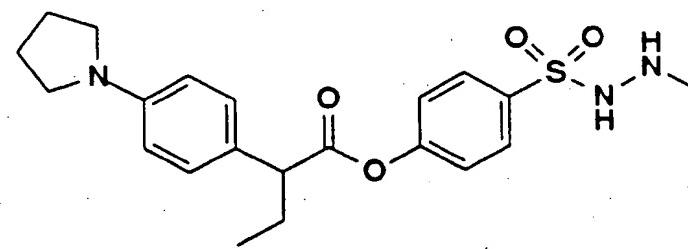
NMR (CDCl_3): δ 7.92 (2H, d, $J=8.7\text{Hz}$), 7.23 (2H, d, $J=8.7\text{Hz}$), 7.15 (2H, d, $J=8.7\text{Hz}$), 6.55 (2H, d, $J=8.7\text{Hz}$), 3.58 (1H, d, $J=7.7\text{Hz}$), 3.29 (4H, t, $J=6.6\text{Hz}$), 2.37 (6H, s), 2.25-1.75 (6H, m), 0.98 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.45 (hexane:ethyl acetate=1:1).

Example 1(55)

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4-(N-(N'-methylamino)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR (CDCl_3): δ 7.82 (2H, d, $J=8.7\text{Hz}$), 7.23 (4H, m), 6.56 (2H, d, $J=8.6\text{Hz}$), 3.60 (1H, m), 3.29 (4H, t, $J=6.6\text{Hz}$), 2.85 (3H, s), 2.25-1.80 (6H, m), 0.99 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.35 (hexane:ethyl acetate=1:1).

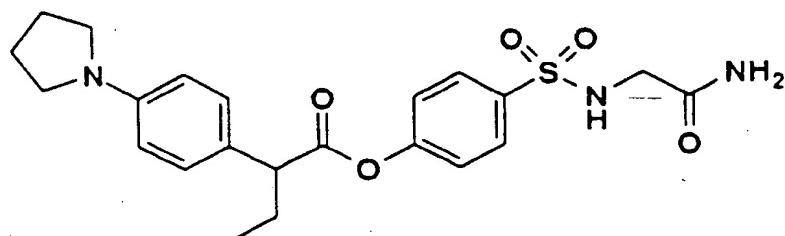
Example 1(56)

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4-(N-(carbamoylmethyl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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EP 0 769 498 A1

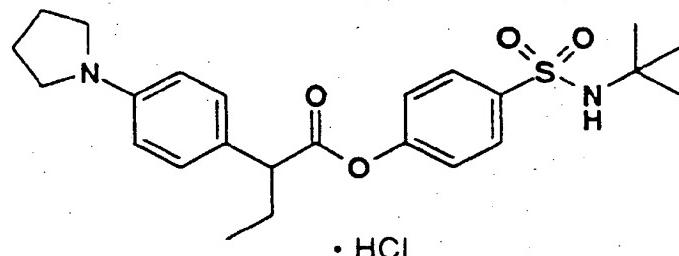
NMR (CDCl_3): δ 7.78 (2H, d, $J=8.7\text{Hz}$), 7.20 (2H, d, $J=8.6\text{Hz}$), 7.11 (2H, d, $J=8.7\text{Hz}$), 6.54 (2H, d, $J=8.6\text{Hz}$), 6.42-6.30 (1H, brs), 6.20-5.96 (2H, m), 3.58 (1H, t, $J=7.8\text{Hz}$), 3.50 (2H, s), 3.38-3.18 (4H, m), 2.26-1.74 (6H, m), 0.96 (3H, t, $J=7.3\text{Hz}$);
 TLC : Rf 0.41 (chloroform:methanol=9:1).

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Example 1(57)

4-(N-t-butylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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NMR (CDCl_3): δ 7.89 (2H, d, $J=8.8\text{Hz}$), 7.63 (2H, d, $J=8.6\text{Hz}$), 7.48 (2H, d, $J=8.6\text{Hz}$), 7.12 (2H, d, $J=8.8\text{Hz}$), 4.83 (1H, s), 3.74 (1H, t, $J=7.6\text{Hz}$), 3.80-3.50 (4H, m), 2.40-2.25 (4H, m), 2.40-2.10 and 2.05-1.75 (each 1H, m), 1.22 (9H, s), 1.00 (3H, t, $J=7.4\text{Hz}$);
 TLC : Rf 0.55 (ethyl acetate:hexane=1:2).

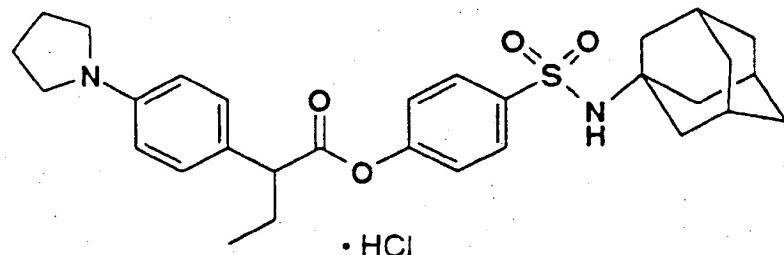
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Example 1(58)

4-(N-adamantan-1-ylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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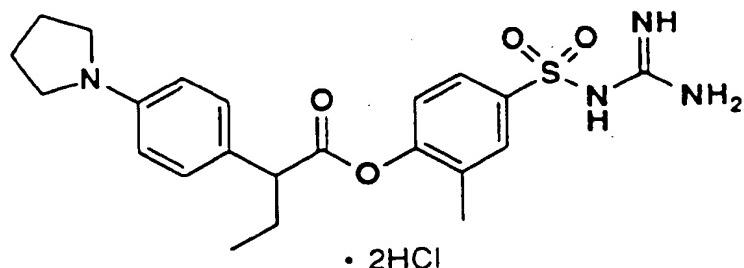
NMR (CDCl_3): δ 7.89 (2H, d, $J=8.6\text{Hz}$), 7.60-7.45 (4H, m), 7.12 (2H, d, $J=8.6\text{Hz}$), 4.64 (1H, brs, NH), 3.80-3.55 (5H, m), 2.40-1.48 (21H, m), 0.999 (3H, t, $J=7.2\text{Hz}$);
 TLC : Rf 0.44 (hexane:ethyl acetate:acetic acid=5:2:0.2).

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Example 1(59)

4-guanidinosulfonyl-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

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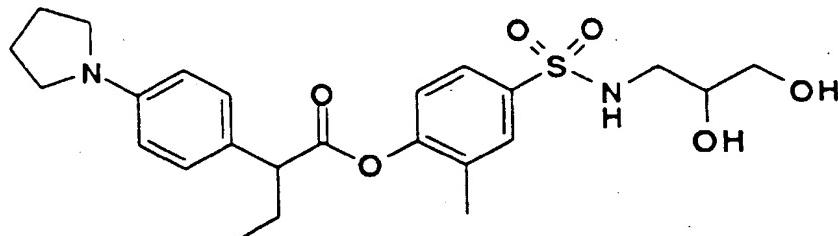
NMR (DMSO-d₆): δ 7.66-7.53 (2H, m), 7.28 (2H, d, J=8.0Hz), 7.04 (1H, d, J=8.0Hz), 7.10-6.50 (6H, m), 3.76 (1H, t, J=7.5Hz), 3.50-3.20 (4H, m), 2.20-1.70 (2H, m), 2.10-1.90 (4H, m), 1.93 (3H, s), 0.91 (3H, t, J=7.5Hz);
15 TLC : Rf 0.36 (water:methanol:chloroform=1:10:90).

Example 1(60)

4-(N-2RS,3-dihydroxypropylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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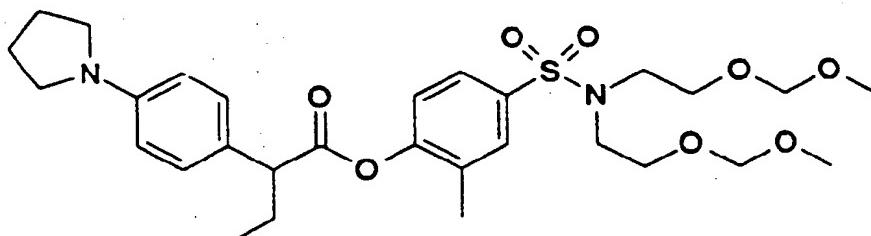
NMR (DMSO-d₆): δ 7.70-7.60 (2H, m), 7.47 (1H, t, J=6.0Hz), 7.18 (2H, d, J=8.5Hz), 7.13 (1H, d, J=8.5Hz), 6.55 (2H, d, J=8.5Hz), 3.70 (1H, t, J=7.5Hz), 3.55-3.35 (6H, m), 2.94-2.78 (1H, m), 2.66-2.54 (1H, m), 2.25-1.60 (2H, m), 2.05-1.90 (4H, m), 1.96 (3H, s), 0.91 (3H, t, J=7.5Hz);
35 TLC : Rf 0.29 (water:methanol:chloroform=1:10:90).

Example 1(61)

4-(N,N-bis(2-(methoxymethoxy)ethyl)sulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid es-
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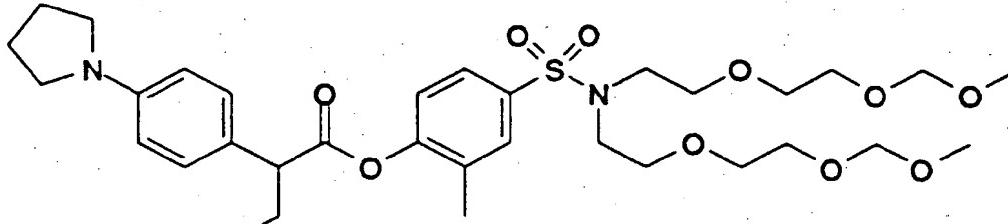
NMR (CDCl₃): δ 7.70-7.58 (2H, m), 7.22 (2H, d, J=9Hz), 7.03 (1H, d, J=8Hz), 6.55 (2H, d, J=9Hz), 4.54 (4H, s), 55 3.67 (4H, t, J=6Hz), 3.60 (1H, t, J=7Hz), 3.43 (4H, t, J=6Hz), 3.35-3.20 (10H, m), 2.30-1.75 (9H, m), 0.99 (3H, t, J=7Hz);
TLC : Rf 0.27 (hexane:ethyl acetate=2:1).

Example 1(62)

4-(N,N-bis(2-(2-(methoxymethoxy)ethoxy)ethyl)sulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR (CDCl_3): δ 7.68-7.58 (2H, m), 7.22 (2H, d, $J=9\text{Hz}$), 7.03 (1H, d, $J=8\text{Hz}$), 6.55 (2H, d, $J=9\text{Hz}$), 4.63 (4H, s), 3.70-3.50 (13H, m), 3.45-3.20 (8H, m), 3.35 (6H, s), 2.30-1.75 (9H, m), 0.99 (3H, t, $J=7\text{Hz}$);

TLC : Rf 0.20 (hexane:ethyl acetate=1:1).

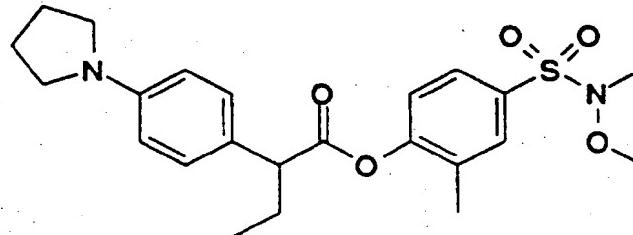
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Example 1(63)

4-(N-methyl-N-methoxysulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR (CDCl_3): δ 7.68 (1H, s), 7.66 (1H, d, $J=8.4\text{Hz}$), 7.22 (2H, d, $J=8.6\text{Hz}$), 7.11 (1H, d, $J=8.4\text{Hz}$), 6.55 (2H, d, $J=8.6\text{Hz}$), 3.78 (3H, s), 3.62 (1H, t, $J=7.7\text{Hz}$), 3.28 (4H, t, $J=6.6\text{Hz}$), 2.76 (3H, s), 2.3-2.1 (1H, m), 2.06 (3H, s), 2.1-1.9 (4H, m), 2.1-1.8 (1H, m), 0.99 (3H, t, $J=7.3\text{Hz}$);

TLC : Rf 0.36 (hexane:ethyl acetate=4:1).

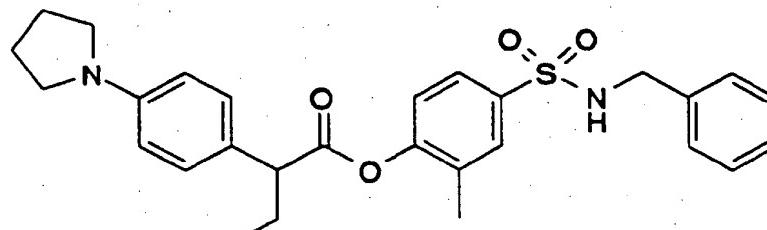
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Example 1(64)

4-(N-benzylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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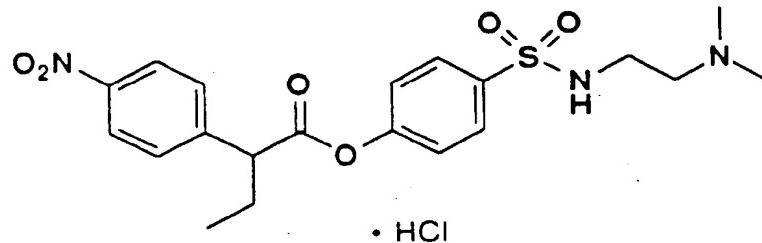
55

NMR (CDCl_3): δ 7.66-7.62 (2H, m), 7.29-7.15 (7H, m), 7.05 (1H, d, $J=9.0\text{Hz}$), 6.55 (2H, d, $J=8.6\text{Hz}$), 4.65 (1H, t, $J=5.6\text{Hz}$), 4.11 (2H, d, $J=5.6\text{Hz}$), 3.62 (1H, t, $J=7.8\text{Hz}$), 3.33-3.26 (4H, m), 2.27-1.82 (6H, m), 2.00 (3H, s), 1.00 (3H, t, $J=7.4\text{Hz}$);

TLC : Rf 0.86 (hexane:ethyl acetate=1:1).

Example 1(65)

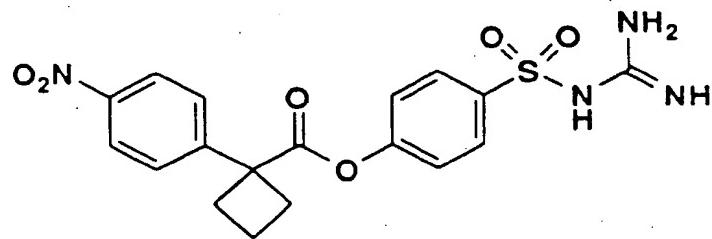
5 4-(N-2-(N',N'-dimethylamino)ethylsulfamoyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester · hydrochloride



20 NMR (CD_3OD): δ 8.27 (2H, d, $J=8.5\text{Hz}$), 7.93 (2H, d, $J=8.5\text{Hz}$), 7.68 (2H, d, $J=8.5\text{Hz}$), 7.28 (2H, d, $J=8.5\text{Hz}$),
4.04 (1H, t, $J=7.6\text{Hz}$), 3.22 (4H, m), 2.93 (6H, s), 2.28 (1H, m), 1.97 (1H, m), 1.00 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.39 (chloroform:methanol:water=9:1:0.1).

Example 1(66)

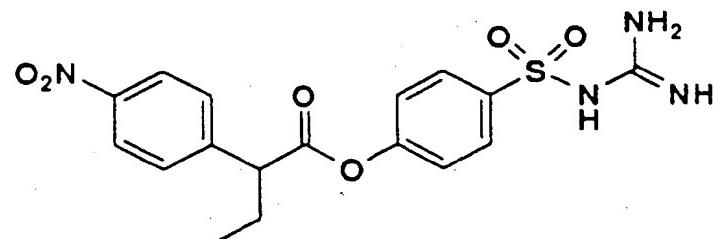
25 4-guanidinosulfonylphenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester



40 NMR (CDCl_3): δ 8.26 (2H, d, $J=8.8\text{Hz}$), 7.85 (2H, d, $J=8.8\text{Hz}$), 7.57 (2H, d, $J=8.8\text{Hz}$), 7.04 (2H, d, $J=8.8\text{Hz}$), 6.34
(1H, brs), 3.14-2.96 (2H, m), 2.77-2.59 (2H, m), 2.38-1.90 (2H, m);
TLC : Rf 0.56 (acetic acid:methanol:chloroform=1:5:25).

45 Example 1(67)

4-guanidinosulfonylphenyl 2RS-(4-nitrophenyl)butanoic acid ester



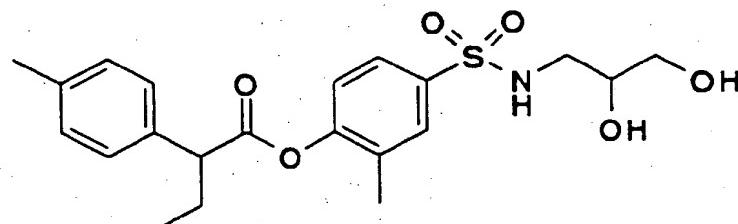
NMR (DMSO-d_6): δ 8.27 (2H, d, $J=8.8\text{Hz}$), 7.78 (2H, d, $J=8.8\text{Hz}$), 7.71 (2H, d, $J=8.8\text{Hz}$), 7.19 (2H, d, $J=8.8\text{Hz}$),
7.0-6.4 (4H, brs), 4.15 (1H, t, $J=7.6\text{Hz}$), 2.30-2.05 and 2.05-1.75 (each 1H, m), 0.92 (3H, t, $J=7.6\text{Hz}$);
TLC : Rf 0.09 (acetic acid:methanol:chloroform=1:2:40).

Example 1(68)

4-(N-2RS,3-dihydroxypropylsulfamoyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester

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NMR (CDCl_3): δ 7.67-7.61 (2H, m), 7.27 (2H, d, $J=8\text{Hz}$), 7.17 (2H, d, $J=8\text{Hz}$), 7.04 (1H, d, $J=8\text{Hz}$), 5.54 (1H, br), 3.80-3.46 (3H, m), 3.42 (1H, br), 3.70 (1H, t, $J=8\text{Hz}$), 3.11-2.87 (2H, m), 2.83 (1H, br), 2.35 (3H, s), 2.32-2.11 and 2.03-1.79 (each 1H, m), 1.98 (3H, s), 0.99 (3H, t, $J=8\text{Hz}$);

TLC : Rf 0.40 (chloroform:methanol:water=9:1:0.1).

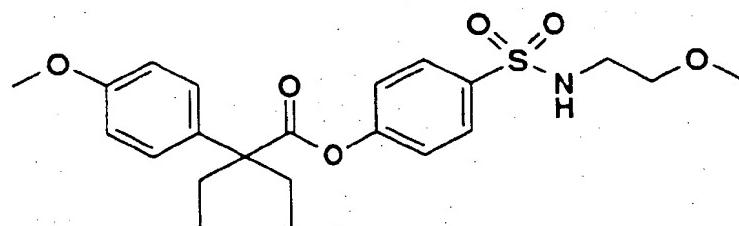
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Example 1(69)

4-(N-2-methoxyethylsulfamoyl)phenyl 2-(4-methoxyphenyl)-2-ethylbutanoic acid ester

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NMR (CDCl_3): δ 7.83 (2H, d, $J=8.8\text{Hz}$), 7.27 (2H, d, $J=8.8\text{Hz}$), 7.08 (2H, d, $J=9.2\text{Hz}$), 6.90 (2H, d, $J=8.8\text{Hz}$), 4.92 (1H, t, $J=6.5\text{Hz}$), 3.82 (3H, s), 3.38 (2H, t, $J=5.4\text{Hz}$), 3.25 (3H, s), 3.11 (2H, t, $J=6.0\text{Hz}$), 2.28-2.04 (4H, m), 0.846 (6H, t, $J=7.4\text{Hz}$);

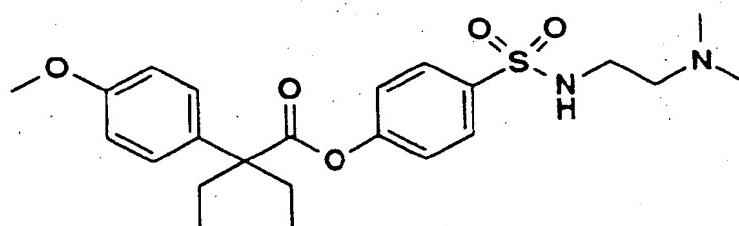
TLC : Rf 0.16 (hexane:ethyl acetate=2:1).

40 Example 1(70)

4-(N-2-(N',N'-dimethylamino)ethylsulfamoyl)phenyl 2-(4-methoxyphenyl)-2-ethylbutanoic acid ester · acetate

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· CH_3COOH

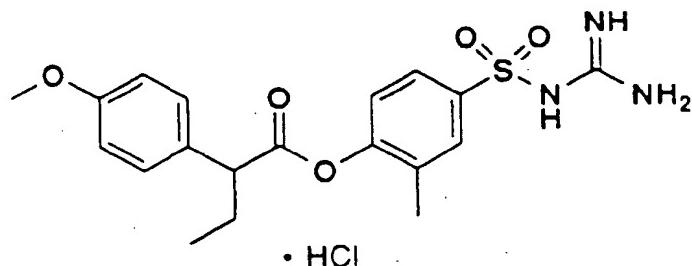
55

NMR (CDCl_3): δ 7.85 (2H, d, $J=8.6\text{Hz}$), 7.28 (2H, d, $J=8.8\text{Hz}$), 7.09 (2H, d, $J=8.6\text{Hz}$), 6.92 (2H, d, $J=8.8\text{Hz}$), 3.83 (3H, s), 2.53-2.47 (4H, m), 2.24 (6H, s), 2.24-2.11 (4H, m), 0.847 (6H, t, $J=7.4\text{Hz}$);

TLC : Rf 0.26 (chloroform:methanol:water=25:5:1).

Example 1(71)

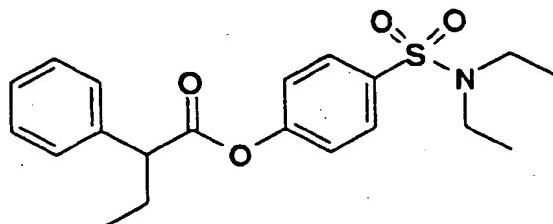
- 5 4-(guanidinosulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester · hydrochloride



NMR (DMSO-d₆): δ 7.62 (1H, s), 7.60 (1H, d, J=8.0Hz), 7.30 (2H, d, J=8.5Hz), 6.96 (1H, d, J=8.0Hz), 6.90 (2H, d, J=8.5Hz), 6.6-6.1 (4H, *brs*), 3.80 (1H, t, J=7.5Hz), 2.3-2.0 and 2.0-1.7 (each 1H, m), 1.65 (3H, s), 0.98 (3H, t, J=7.5Hz);
TLC : Rf 0.60 (water:methanol:chloroform=1:10:40).

Example 1(72)

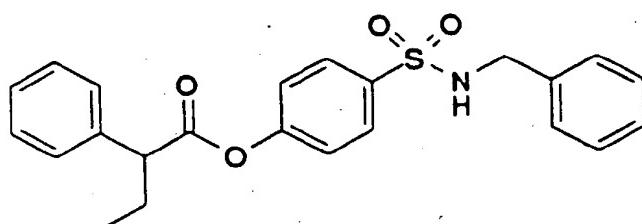
- 25 4-(N,N-diethylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester



NMR (CDCl_3): δ 7.83-7.73 (2H, m), 7.40-7.23 (5H, m), 7.16-7.07 (2H, m), 3.69 (1H, t, $J=7\text{Hz}$), 3.20 (4H, q, $J=7\text{Hz}$), 2.35-1.75 (2H, m), 1.11 (6H, t, $J=7\text{Hz}$), 0.98 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.39 (hexane:ethyl acetate=7:3).

Example 1(73)

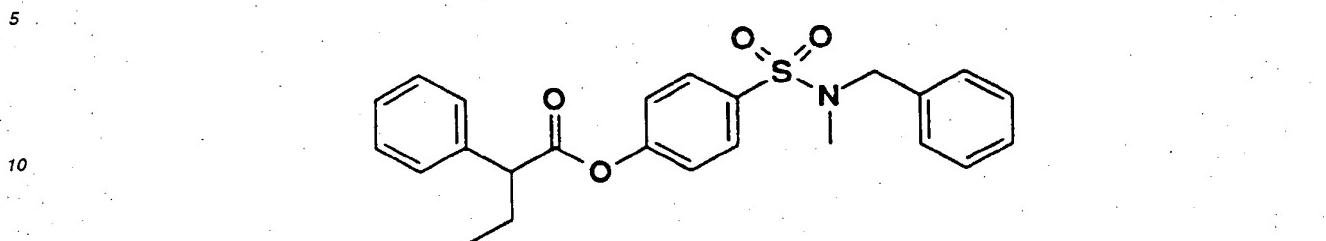
- 4-(N-benzylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester



NMR (CDCl_3): δ 7.89-7.79 (2H, m), 7.42-7.08 (12H, m), 4.61 (1H, t, $J=7\text{Hz}$), 4.13 (2H, d, $J=7\text{Hz}$), 3.70 (1H, t, $J=7\text{Hz}$), 2.36-2.11 (1H, m), 2.05-1.80 (1H, m), 0.99 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.41 (hexane:ethyl acetate=2:1).

Example 1(74)

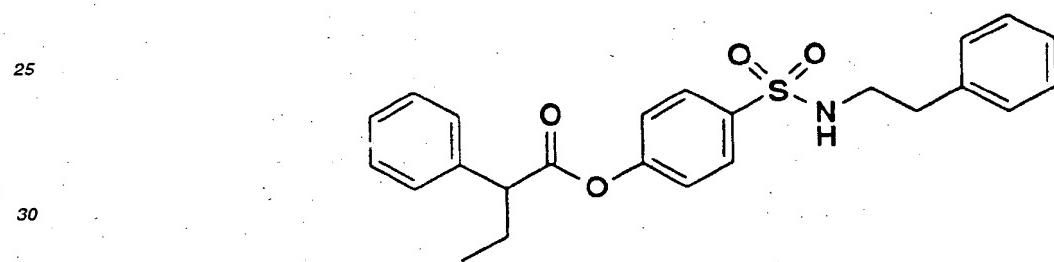
4-(N-methyl-N-benzylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester



15 NMR (CDCl_3): δ 7.86-7.76 (2H, m), 7.43-7.14 (12H, m), 4.11 (2H, s), 3.73 (1H, t, $J=7\text{Hz}$), 2.59 (3H, s), 2.38-2.13 (1H, m), 2.06-1.81 (1H, m), 1.01 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.57 (hexane:ethyl acetate=2:1).

Example 1(75)

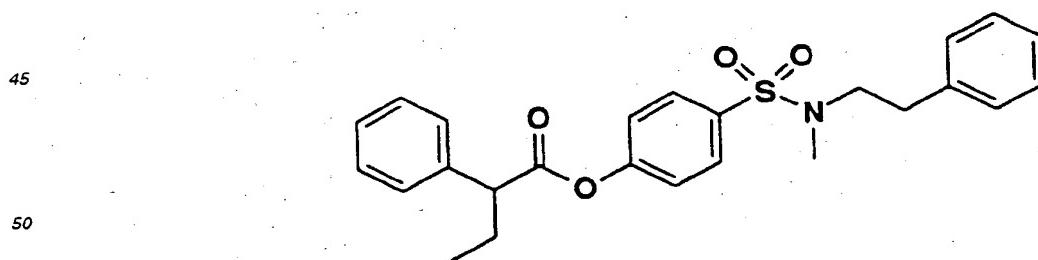
4-(N-2-phenylethylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester



35 NMR (CDCl_3): δ 7.81-7.71 (2H, m), 7.43-7.03 (12H, m), 4.40 (1H, t, $J=7\text{Hz}$), 3.71 (1H, t, $J=7\text{Hz}$), 3.21 (2H, q, $J=7\text{Hz}$), 2.76 (2H, t, $J=7\text{Hz}$), 2.24 (1H, ddq, $J=14\text{Hz}, 7\text{Hz}, 7\text{Hz}$), 1.93 (1H, ddq, $J=14\text{Hz}, 7\text{Hz}, 7\text{Hz}$), 1.00 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.46 (hexane:ethyl acetate=3:2).

Example 1(76)

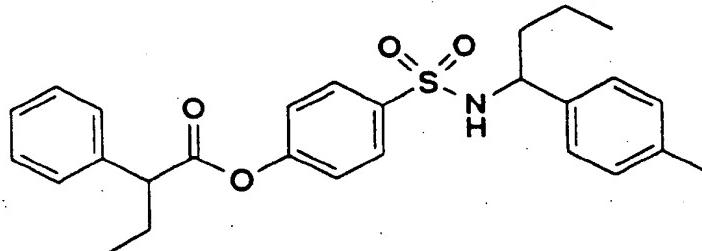
4-(N-methyl-N-2-phenylethylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester



55 NMR (CDCl_3): δ 7.77-7.68 (2H, m), 7.41-7.08 (12H, m), 3.71 (1H, t, $J=7\text{Hz}$), 3.33-3.18 (2H, m), 2.92-2.79 (2H, m), 2.73 (3H, s), 2.24 (1H, ddq, $J=14\text{Hz}, 7\text{Hz}, 7\text{Hz}$), 1.92 (1H, ddq, $J=14\text{Hz}, 7\text{Hz}, 7\text{Hz}$), 0.99 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.32 (hexane:ethyl acetate=3:2).

Example 1(77)

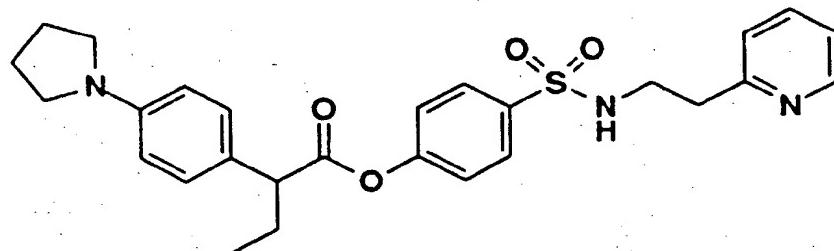
4-(N-1RS-(4-methylphenyl)butylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester



NMR (CDCl_3): δ 7.55 (2H, d, $J=8\text{Hz}$), 7.41-7.23 (5H, m), 6.98-6.78 (6H, m), 4.81 (1H, d, $J=7\text{Hz}$), 4.23 (1H, q, $J=7\text{Hz}$), 3.68 (1H, t, $J=7\text{Hz}$), 2.35-2.08 (1H, m), 2.20 (3H, s), 1.91 (1H, ddq, $J=14\text{Hz}, 7\text{Hz}, 7\text{Hz}$), 1.79-1.52 (2H, m), 1.38-1.06 (2H, m), 0.99 (3H, t, $J=7\text{Hz}$), 0.83 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.15 (hexane:ethyl acetate=4:1).

Example 1(78)

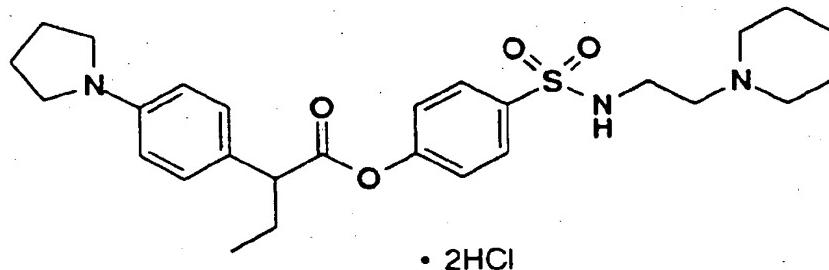
4-(N-2-(pyridin-2-yl)ethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride



NMR (DMSO-d_6): δ 8.79 (1H, d, $J=5.0\text{Hz}$), 8.50 (1H, t, $J=7.4\text{Hz}$), 8.04 (1H, m), 7.90 (2H, m), 7.79 (2H, d, $J=8.6\text{Hz}$), 7.28 (2H, m), 7.21 (2H, d, $J=8.4\text{Hz}$), 6.90 (2H, m), 3.76 (1H, t, $J=7.0\text{Hz}$), 3.34 (4H, brs), 3.23 (4H, brs), 2.01 (5H, m), 1.80 (1H, m), 0.91 (3H, t, $J=7.0\text{Hz}$);
TLC : Rf 0.48 (chloroform:methanol:water=9:1:0.1).

Example 1(79)

4-(N-2-(piperidin-1-yl)ethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride



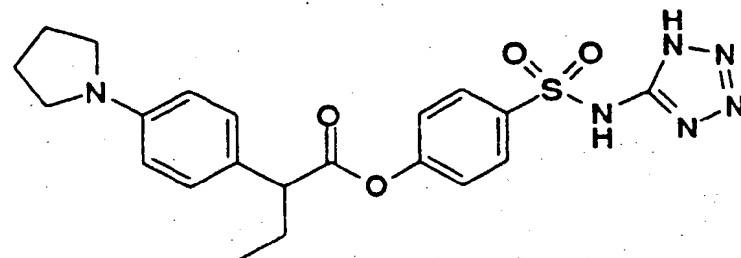
NMR (CD_3OD): δ 7.92 (2H, d, $J=8.8\text{Hz}$), 7.71 (2H, d, $J=8.8\text{Hz}$), 7.63 (2H, d, $J=8.8\text{Hz}$), 7.26 (2H, d, $J=8.8\text{Hz}$), 3.95 (1H, t, $J=7.2\text{Hz}$), 3.81 (4H, m), 3.55 (2H, brd, $J=12.0\text{Hz}$), 3.24 (4H, brs), 2.98 (2H, brt, $J=12.0\text{Hz}$), 2.32 (4H, m), 1.89 (7H, m), 1.55 (1H, m), 0.99 (3H, t, $J=7.2\text{Hz}$);
TLC : Rf 0.39 (chloroform:methanol:water=9:1:0.1).

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Example 1(80)

4-(N-(tetrazol-5-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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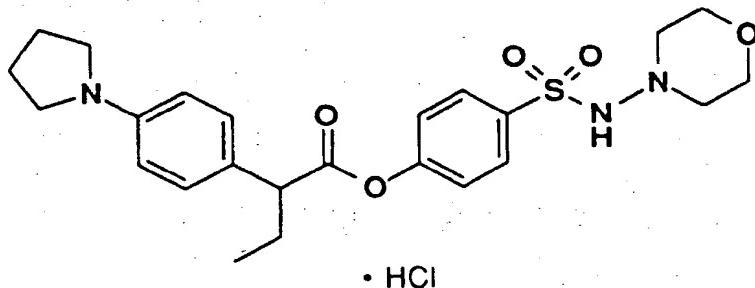
NMR (CD_3OD): δ 7.89 (2H, d, $J=8.6\text{Hz}$), 7.15 (2H, d, $J=8.6\text{Hz}$), 7.02 (2H, d, $J=8.6\text{Hz}$), 6.55 (2H, d, $J=8.6\text{Hz}$), 3.58 (1H, t, $J=7.8\text{Hz}$), 3.35-3.15 (4H, m), 2.20-1.95 and 1.95-1.70 (each 1H, m), 2.05-1.95 (4H, m), 0.93 (3H, t, $J=7.2\text{Hz}$);
TLC : Rf 0.46 (acetic acid:methanol:chloroform=1:5:25).

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Example 1(81)

4-(N-(morpholin-4-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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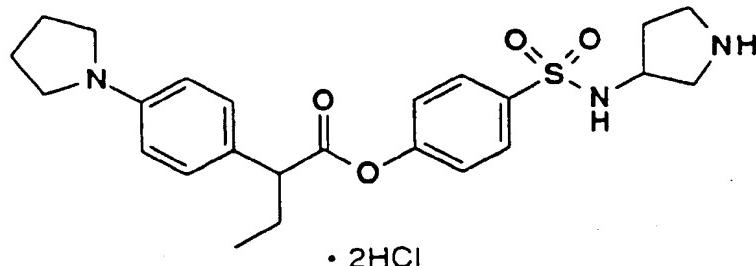
40

NMR (CDCl_3): δ 7.97 (2H, d, $J=8.6\text{Hz}$), 7.61 (2H, d-like), 7.48 (2H, d-like), 7.16 (2H, d, $J=8.6\text{Hz}$), 5.99 (1H, s), 3.74 (1H, t, $J=7.8\text{Hz}$), 3.76-3.63 (4H, m), 3.65-3.54 (4H, m), 2.70-2.58 (4H, m), 2.42-2.29 (4H, m), 2.37-2.10 and 2.04-1.77 (each 1H, m), 1.00 (3H, t, $J=7.2\text{Hz}$);
TLC : Rf 0.45 (methanol:chloroform=1:20).

Example 1(82)

50 4-(N-(pyrrolidin-3-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

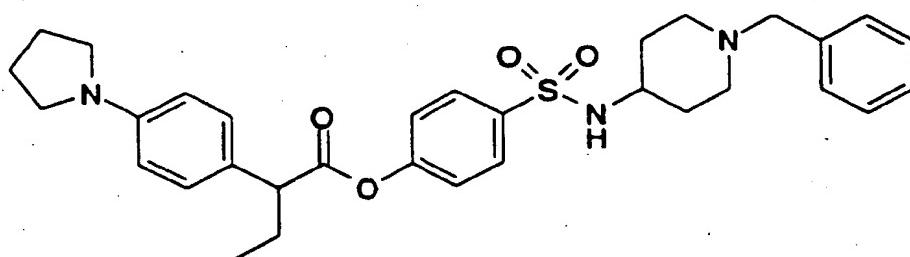
55



15 NMR (CDCl_3): δ 7.7-7.5 (4H, m), 7.42 (2H, d, $J=8.6\text{Hz}$), 6.96 and 6.92 (2H, d, $J=8.6\text{Hz}$), 4.35-4.13 (1H, m), 3.5-2.9 (10H, m), 2.40-2.25 (4H, m), 2.20-1.55 (4H, m), 0.94 (3H, t, $J=7.2\text{Hz}$);
TLC : Rf 0.35 (methanol:chloroform=1:10).

Example 1(83)

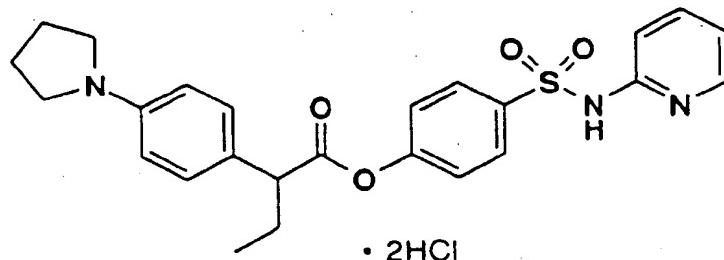
20 4-(N-(1-benzylpiperidin-4-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



35 NMR (CDCl_3): δ 7.82 (2H, d, $J=9.0\text{Hz}$), 7.36-7.08 (5H, m), 7.21 (2H, d, $J=9.0\text{Hz}$), 7.13 (2H, d, $J=8.8\text{Hz}$), 6.55 (2H, d, $J=8.8\text{Hz}$), 4.50 (1H, d, $J=5.7\text{Hz}$), 3.58 (1H, t, $J=5.0\text{Hz}$), 3.43 (2H, s), 3.36-3.21 (4H, m), 3.21-3.02 (1H, m), 2.78-2.61 (2H, m), 2.28-1.65 (10H, m), 1.56-1.34 (1H, m), 0.97 (3H, t, $J=7.2\text{Hz}$);
TLC : Rf 0.60 (ethyl acetate:hexane=9:1).

Example 1(84)

40 4-(N-(pyridin-2-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride



55 NMR (CDCl_3): δ 8.26 (1H, d, $J=6.0\text{Hz}$), 7.96 (2H, d, $J=8.6\text{Hz}$), 7.83 (1H, t, $J=8.6\text{Hz}$), 7.72 (2H, d, $J=8.6\text{Hz}$), 7.55 (1H, d, $J=8.6\text{Hz}$), 7.48 (2H, d, $J=8.6\text{Hz}$), 7.12 (2H, d, $J=8.6\text{Hz}$), 6.95 (1H, t, $J=6.0\text{Hz}$), 3.74 (1H, t, $J=7.6\text{Hz}$), 3.80-3.60 (4H, m), 2.44-2.24 (4H, m), 2.32-2.02 and 2.02-1.72 (each 1H, m), 0.97 (3H, t, $J=7.2\text{Hz}$);
TLC : Rf 0.51 (ethyl acetate:hexane=2:1).

Example 1(85)

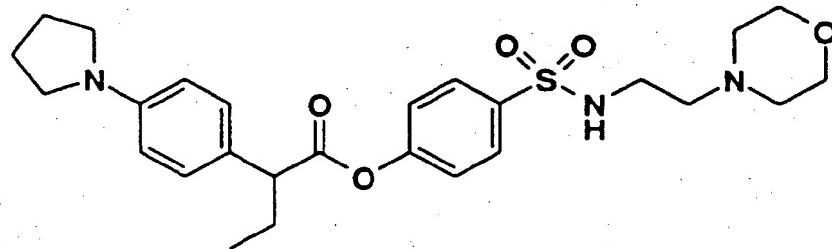
4-(N-2-(morpholin-4-yl)ethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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Example 1(86)

4-(N-(pyrazin-2-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 3hydrochloride

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• 3HCl

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NMR (CDCl₃): δ 7.83 (2H, d, J=8.9Hz), 7.21 (2H, d, J=8.7Hz), 7.13 (2H, d, J=8.9Hz), 6.55 (2H, d, J=8.7Hz), 6.23-5.06 (1H, brs), 3.64-3.52 (5H, m), 3.36-3.20 (4H, m), 2.98 (2H, t, J=6.0Hz), 2.38 (2H, t, J=6.0Hz), 2.30-2.20 (4H, m) 2.20-1.70 (6H, m), 0.97 (3H, t, J=7.2Hz);
TLC : Rf 0.24 (ethyl acetate:hexane=7:3).

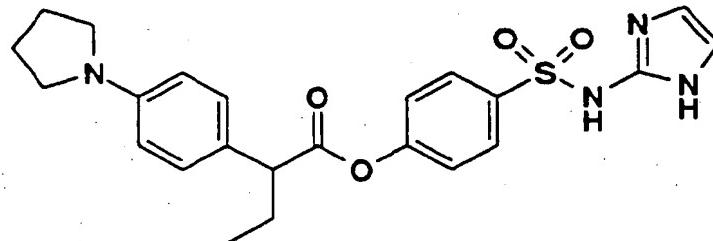
Example 1(87)

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4-(N-(imidazol-2-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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EP 0 769 498 A1

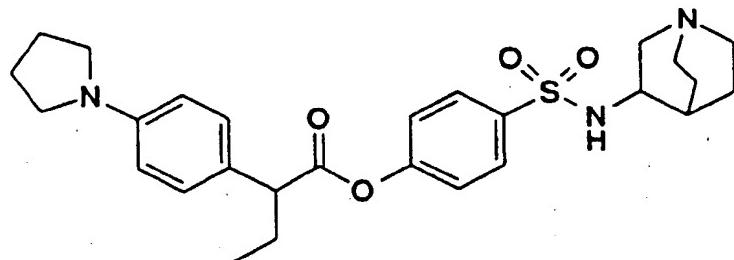
NMR (CDCl_3): δ 7.90 (2H, d, $J=8.8\text{Hz}$), 7.19 (4H, d, $J=8.8\text{Hz}$), 6.81 (1H, d, $J=2.0\text{Hz}$), 6.54 (1H, d, $J=2.0\text{Hz}$), 6.54 (2H, d, $J=8.8\text{Hz}$), 3.57 (1H, t, $J=7.8\text{Hz}$), 3.28 (4H, t-like), 2.30-2.00 and 2.00-1.70 (each 1H, m), 2.00 (4H, t-like), 0.96 (3H, t, $J=7.4\text{Hz}$);
 TLC : Rf 0.67 (methanol:chloroform=1:10).

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Example 1(88)

4-(N-(quinuclidin-3RS-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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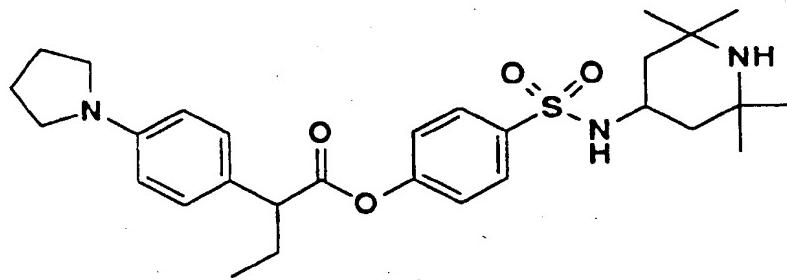
NMR (CDCl_3): δ 7.88 (2H, d, $J=8.8\text{Hz}$), 7.21 (2H, d, $J=8.8\text{Hz}$), 7.11 (2H, d, $J=8.8\text{Hz}$), 6.55 (2H, d, $J=8.8\text{Hz}$), 3.58 (1H, t, $J=7.6\text{Hz}$), 3.60-3.47 (1H, m), 3.35-3.20 (4H, m), 3.30-2.80 (6H, m), 2.10-1.95 (4H, m), 2.30-1.40 (7H, m), 0.98 (3H, t, $J=7.2\text{Hz}$);

25 TLC : Rf 0.43 (acetic acid:methanol:chloroform=1:5:25).

Example 1(89)

4-(N-(2,2,6,6-tetramethylpiperidin-4-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR ($\text{CDCl}_3+\text{CD}_3\text{OD}$): δ 7.85 (2H, d, $J=8.8\text{Hz}$), 7.22 (2H, d, $J=8.6\text{Hz}$), 7.14 (2H, d, $J=8.8\text{Hz}$), 6.57 (2H, d, $J=8.6\text{Hz}$), 3.59 (1H, t, $J=7.8\text{Hz}$), 3.60-3.42 (1H, m), 3.35-3.20 (4H, m), 2.30-1.75 (2H, m), 2.06-1.96 (4H, m), 1.63 (2H, dd, $J=13.2$ and 3.8Hz), 1.33-1.08 (2H, m), 1.19 (12H, s), 0.98 (3H, t, $J=7.3\text{Hz}$);

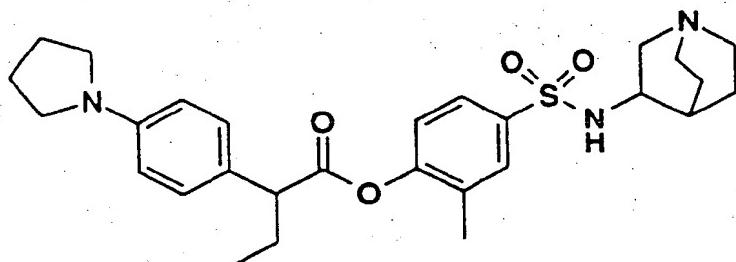
TLC : Rf 0.55 (chloroform:methanol:acetic acid=25:5:1).

Example 1(90)

50 4-(N-(quinuclidin-3RS-yl)sulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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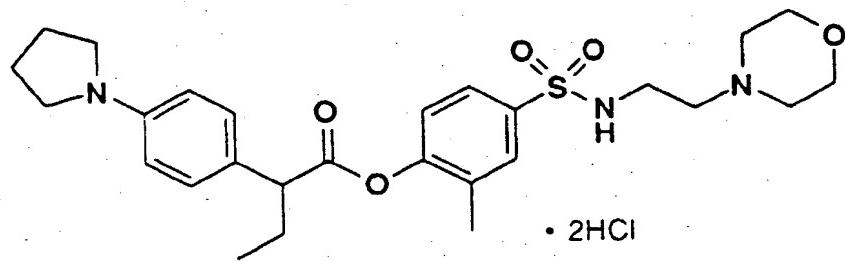
15 NMR (CDCl_3): δ 7.69 (1H, d, $J=2\text{Hz}$), 7.66 (1H, dd, $J=8$ and 2Hz), 7.30-7.13 (2H, m), 7.06 (1H, d, $J=8\text{Hz}$), 6.55 (2H, d, $J=9\text{Hz}$), 3.62 (1H, t, $J=8\text{Hz}$), 3.38-3.23 (5H, m), 3.23-3.05 (1H, m), 2.90-2.48 (5H, m), 2.32-2.08 (1H, m), 2.04 (3H, s), 2.08-1.03 (10H, m), 0.99 (3H, t, $J=7\text{Hz}$);

TLC : Rf 0.43 (chloroform:methanol:water=8:2:0.2).

Example 1(91)

20 4-(N-2-(morpholin-4-yl)ethylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
2hydrochloride

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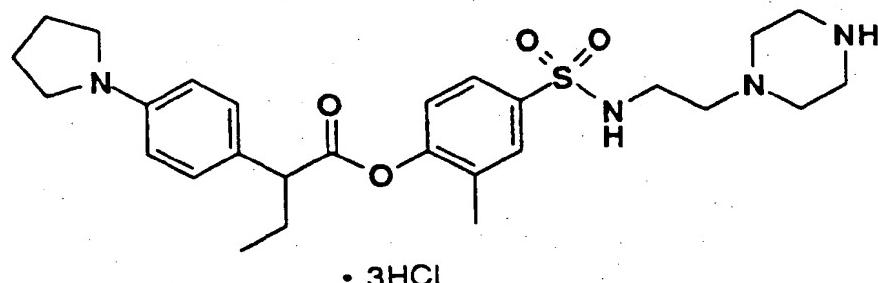
35 NMR (DMSO-d_6): δ 11.3-11.1 (1H, brs), 8.18 (1H, brs), 7.75 (1H, s), 7.70 (1H, d, $J=8.0\text{Hz}$), 7.27 (2H, d, $J=8.6\text{Hz}$),
7.18 (2H, d, $J=9.2\text{Hz}$), 4.0-3.7 (5H, m), 3.4-3.0 (12H, m), 2.2-2.0 (1H, m), 2.1-1.9 (4H, brs), 2.0-1.7 (1H, m), 1.98 (3H,
s), 0.91 (3H, t, $J=7.3\text{Hz}$);

TLC : Rf 0.50 (chloroform:methanol=9:1).

40 Example 1(92)

4-(N-2-(piperazin-4-yl)ethylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
3hydrochloride

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NMR (DMSO-d_6): δ 9.6-9.2 (2H, br), 7.71 (1H, s), 7.67 (1H, d, $J=8.0\text{Hz}$), 7.18 (2H, d, $J=8.4\text{Hz}$), 7.14 (1H, d,

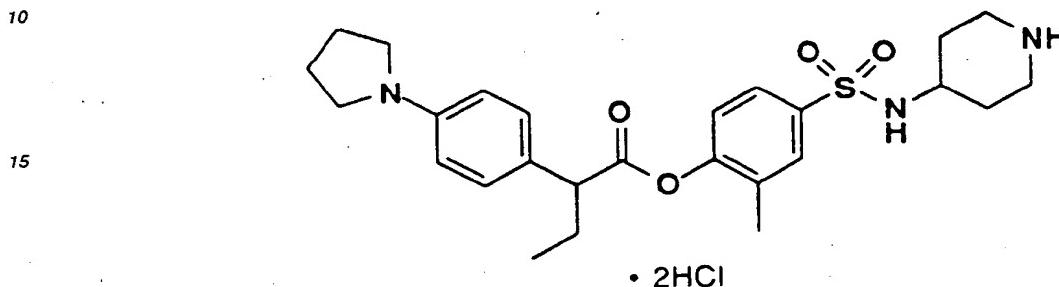
EP 0 769 498 A1

J=8.0Hz), 6.53 (2H, d, J=8.4Hz), 3.69 (1H, t, J=7.3Hz), 3.7-2.6 (16H, br), 2.2-2.0 (1H, m), 2.0-1.9 (4H, brs), 1.96 (3H, s), 1.9-1.7 (1H, m), 0.90 (3H, t, J=7.1Hz);

TLC : Rf 0.46 (chloroform:methanol:acetic acid=25:5:1).

5 Example 1(93)

4-(N-(piperidin-4-yl)sulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

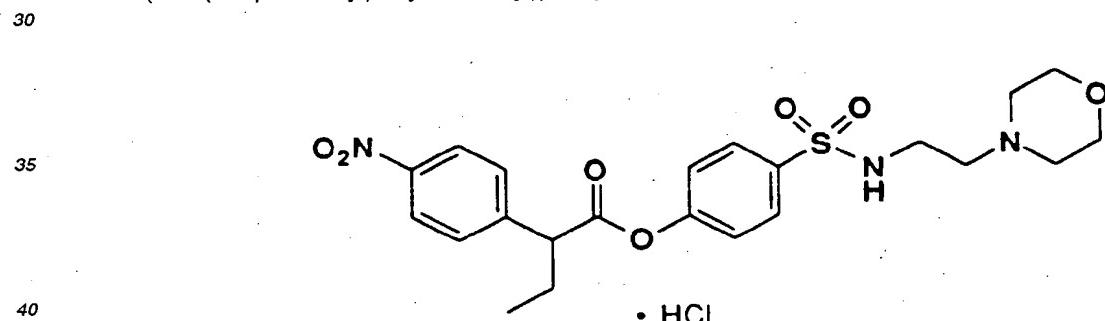


NMR (DMSO-d₆): δ 9.1-8.7 (1H, br), 8.00 (1H, d, J=7.2Hz), 7.71 (1H, s), 7.68 (1H, d, J=8.4Hz), 7.26 (2H, d, J=8.4Hz), 7.15 (1H, d, J=8.4Hz), 6.79 (2H, d, J=8.4Hz), 3.76 (1H, t, J=7.8Hz), 3.4-3.2 (4H, brs), 3.2-3.0 (3H, br), 3.0-2.7 (2H, br), 2.2-1.9 (1H, m), 1.99 (4H, brs), 1.97 (3H, s), 1.9-1.5 (5H, m), 0.91 (3H, t, J=7.3Hz);

TLC : Rf 0.46 (chloroform:methanol:acetic acid=25:5:1).

Example 1(94)

4-(N-2-(morpholin-4-yl)ethylsulfamoyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester · hydrochloride



NMR (CD₃OD): δ 8.27 (2H, d, J=8.6Hz), 7.92 (2H, d, J=9.0Hz), 7.67 (2H, d, J=8.6Hz), 7.27 (2H, d, J=9.0Hz), 4.03 (1H, t, J=7.6Hz), 3.90 (2H, m), 3.50 (2H, m), 3.28 (8H, m), 2.28 (1H, m), 1.99 (1H, m), 1.00 (3H, t, J=7.4Hz);

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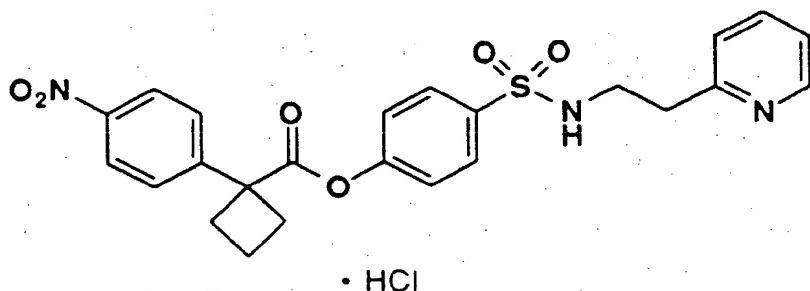
TLC : Rf 0.61 (chloroform:methanol:water=9:1:0.1).

Example 1(95)

4-(N-2-(pyridin-2-yl)ethylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester · hydrochloride

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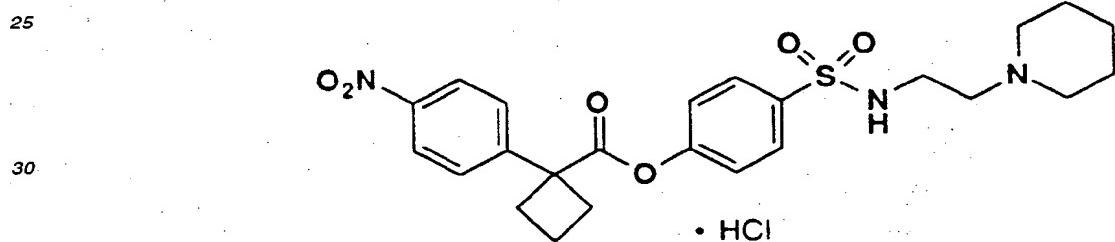
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15 NMR (CD₃OD): δ 8.72 (1H, d, J=8.0Hz), 8.53 (1H, t, J=8.0Hz), 8.28 (2H, d, J=8.6Hz), 7.96 (1H, d, J=8.0Hz), 7.93 (1H, d, J=8.0Hz), 7.79 (2H, d, J=8.6Hz), 7.66 (2H, d, J=8.6Hz), 7.17 (2H, d, J=8.6Hz), 3.30 (4H, m), 3.06 (2H, m), 2.72 (2H, m), 2.23 (1H, m), 2.04 (1H, m);
TLC : R_f 0.54 (chloroform:methanol:water=9:1:0.1).

Example 1(96)

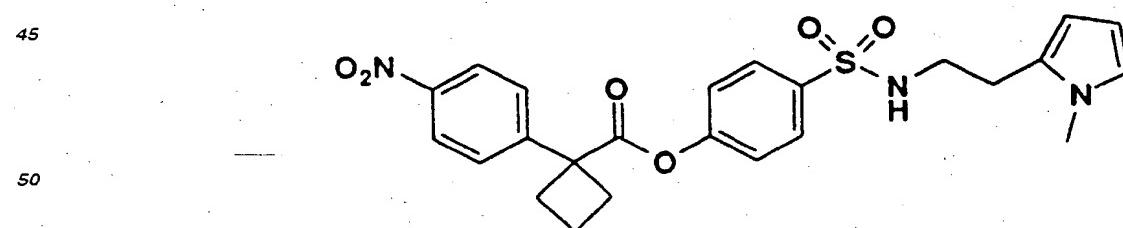
20 4-(N-2-(piperidin-1-yl)ethylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutane carboxylic acid ester · hydrochloride



35 NMR (CD₃OD): δ 8.28 (2H, d, J=8.4Hz), 7.90 (2H, d, J=8.4Hz), 7.66 (2H, d, J=8.4Hz), 7.23 (2H, d, J=8.4Hz), 3.50 (2H, m), 3.30 (4H, m), 3.06 (4H, m), 2.73 (2H, m), 2.22 (1H, m), 1.99 (1H, m), 1.87 (6H, m);
TLC : R_f 0.45 (chloroform:methanol:water=9:1:0.1).

Example 1(97)

40 4-(N-2-(1-methylpyrrol-2-yl)ethylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutane carboxylic acid ester



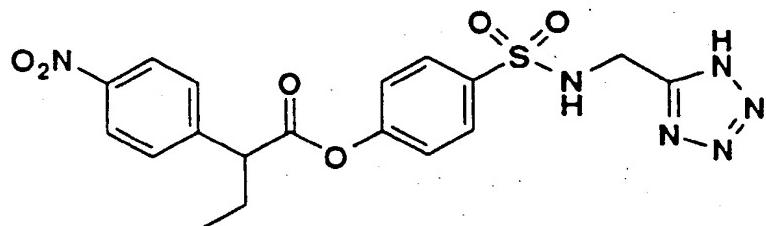
55 NMR (CDCl₃): δ 8.26 (2H, d, J=9.0Hz), 7.78 (2H, d, J=9.0Hz), 7.56 (2H, d, J=9.0Hz), 7.09 (2H, d, J=9.0Hz), 6.52 (1H, dd, J=2.0, 2.4Hz), 6.01 (1H, dd, J=2.4, 2.6Hz), 5.80 (1H, m), 4.64 (1H, t, J=6.6Hz), 3.42 (3H, s), 3.16 (2H, q, J=6.6Hz), 3.05 (2H, m), 2.74 (2H, t, J=6.6Hz), 2.66 (2H, m), 2.25 (1H, m), 2.03 (1H, m);
TLC : R_f 0.26 (hexane:ethyl acetate=2:1).

Example 1(98)

4-(N-(tetrazol-5-ylmethyl)sulfamoyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester

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NMR (DMSO-d₆): δ 8.54 (1H, t, J=5.8Hz), 8.28 (2H, d, J=8.8Hz), 7.85 (2H, d, J=8.8Hz), 7.73 (2H, d, J=8.8Hz), 7.32 (2H, d, J=8.8Hz), 4.30 (2H, d, J=5.8Hz), 4.17 (1H, t, J=7.6Hz), 2.35-2.05 and 2.03-1.75 (each 1H, m), 0.92 (3H, t, J=7.2Hz);

TLC : Rf 0.45 (acetic acid:methanol:chloroform=1:5:25).

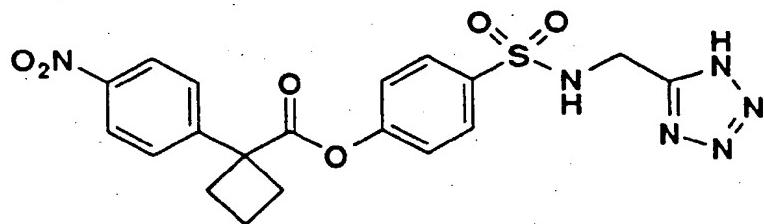
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Example 1(99)

4-(N-(tetrazol-5-ylmethyl)sulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester

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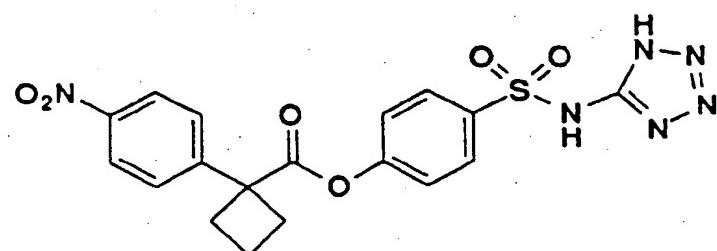
NMR (CD₃OD): δ 8.28 (2H, d, J=8.8Hz), 7.85 (2H, d, J=8.8Hz), 7.67 (2H, d, J=8.8Hz), 7.19 (2H, d, J=8.8Hz), 4.37 (2H, s), 3.16-2.96 (2H, m), 2.82-2.62 (2H, q-like), 2.37-2.12 and 2.12-1.90 (each 1H, m);
TLC : Rf 0.11 (acetic acid:methanol:chloroform=1:2:40).

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Example 1(100)

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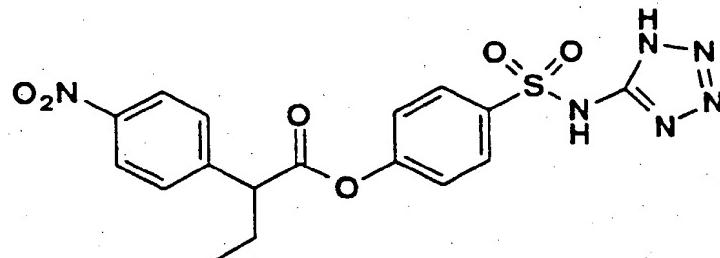
NMR (DMSO-d₆): δ 8.26 (2H, d, J=8.8Hz), 7.84 (2H, d, J=8.8Hz), 7.69 (2H, d, J=8.8Hz), 7.12 (2H, d, J=8.8Hz), 3.08-2.88 (2H, m), 2.74-2.54 (2H, q-like), 2.24-2.04 and 2.04-1.84 (each 1H, m);
TLC : Rf 0.29 (acetic acid:methanol:chloroform=1:5:25).

Example 1(101)

4-(N-(tetrazol-5-yl)sulfamoyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester

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NMR (DMSO-d₆): δ 13.88 (1H, brs), 8.26 (2H, d, J=8.8Hz), 7.82 (2H, d, J=8.8Hz), 7.70 (2H, d, J=8.8Hz), 7.06 (2H, d, J=8.8Hz), 4.12 (1H, t, J=7.4Hz), 2.30-2.00 and 2.00-1.70 (each 1H, m), 0.91 (3H, t, J=7.2Hz);

TLC : Rf 0.26 (acetic acid:methanol:chloroform=1:2:40).

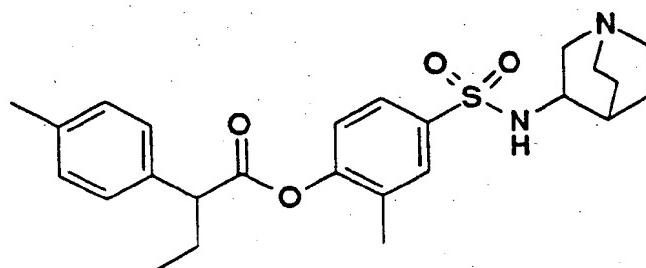
20

Example 1(102)

4-(N-(quinuclidin-3RS-yl)sulfamoyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester

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NMR (CDCl₃): δ 7.70 (1H, d, J=2Hz), 7.67 (1H, dd, J=8 and 2Hz), 7.27 (2H, d, J=8Hz), 7.18 (2H, d, J=8Hz), 7.06 (1H, d, J=8Hz), 3.70 (1H, t, J=8Hz), 3.38-3.23 (1H, m), 3.23-3.05 (1H, m), 2.90-2.49 (5H, m), 2.36 (3H, s), 2.35-2.11 (1H, m), 2.00 (3H, s), 2.05-1.22 (6H, m), 1.00 (3H, t, J=7Hz);

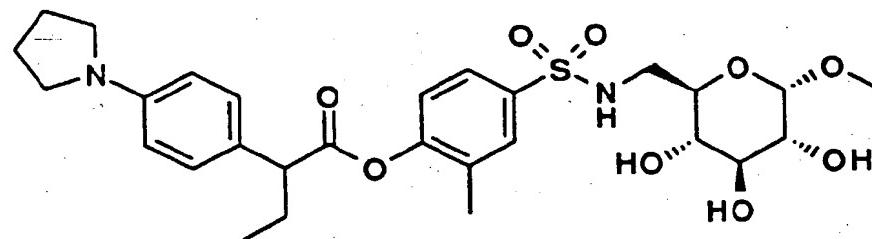
TLC : Rf 0.40 (chloroform:methanol:water=8:2:0.2).

Example 1(103)

4-(N-2R-methoxy-3R-hydroxy-4S-hydroxy-5R-hydroxyperhydropyran-6R-ylmethylsulfamoyl)-2-methylphenyl
45 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR (CDCl₃+6 drops of CD₃OD): δ 7.68-7.63 (m, 2H), 7.22 (d, J=8.8Hz, 2H), 7.05 (d, J=8.1Hz, 1H), 6.55 (d,

EP 0 769 498 A1

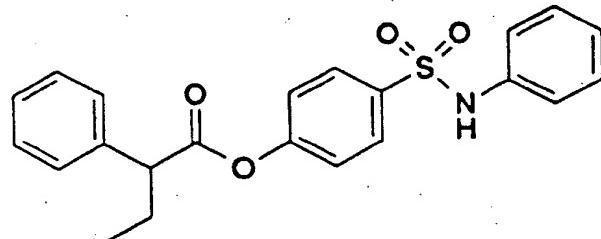
J=8.8Hz, 2H), 4.63 (d, J=3.7Hz, 1H), 3.70-3.50 (m, 3H), 3.50-3.10 (m, 11H), 2.30-1.80 (m, 9H), 0.99 (t, J=7.4Hz, 3H);
 TLC : Rf 0.41 (chloroform:methanol=8:1).

Example 1(104)

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4-(N-phenylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester

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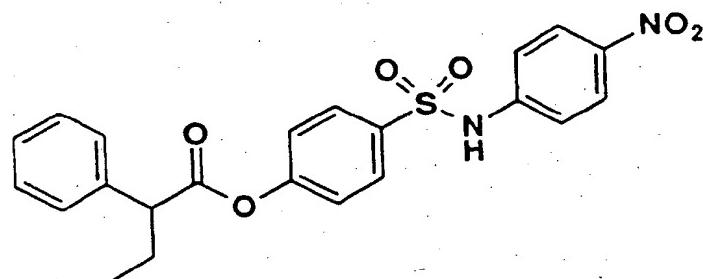
NMR (CDCl₃): δ 7.73 (2H, dd, J=2Hz, 8Hz), 7.40-7.16 (7H, m), 7.16-7.00 (5H, m), 6.76 (1H, s), 3.67 (1H, t, J=7Hz), 2.20 (1H, m), 1.89 (1H, m), 0.96 (3H, t, J=7Hz);
 TLC : Rf 0.57 (hexane:ethyl acetate=1:1).

Example 1(105)

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4-(N-4-nitrophenylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester

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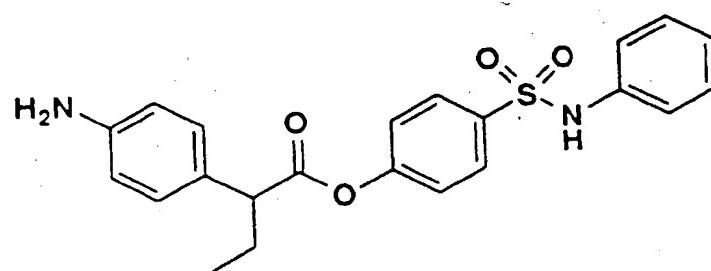
NMR (CDCl₃): δ 8.10 and 7.85 (each 2H, dd, J=2Hz, 8Hz), 7.75 (1H, brs), 7.35 (5H, m), 7.20 and 7.14 (each 2H, dd, J=2Hz, J=8Hz), 3.69 (1H, t, J=7Hz), 2.20 and 1.90 (each 1 H, m), 0.96 (3H, t, J=7Hz);
 TLC : Rf 0.59 (hexane:ethyl acetate=1:1).

Example 1(106)

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4-(N-phenylsulfamoyl)phenyl 2RS-(4-aminophenyl)butanoic acid ester

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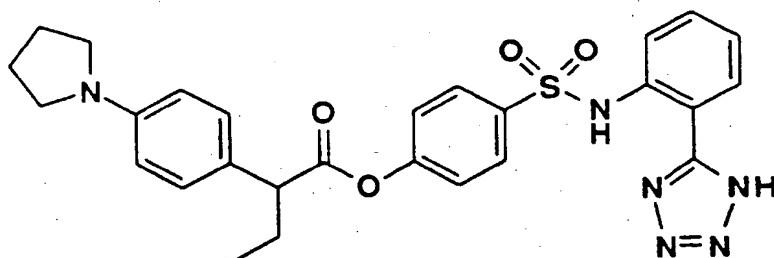
55

NMR (DMSO-d₆): δ 7.72 (2H, d, J=8Hz), 7.42-6.91 (9H, m), 6.80-6.54 (3H, m), 3.56 (1H, t, J=7Hz), 2.23-1.64

(2H, m), 0.92 (3H, t; J=7Hz);
 TLC : Rf 0.39 (hexane:ethyl acetate=1:1).

Example 1(107)

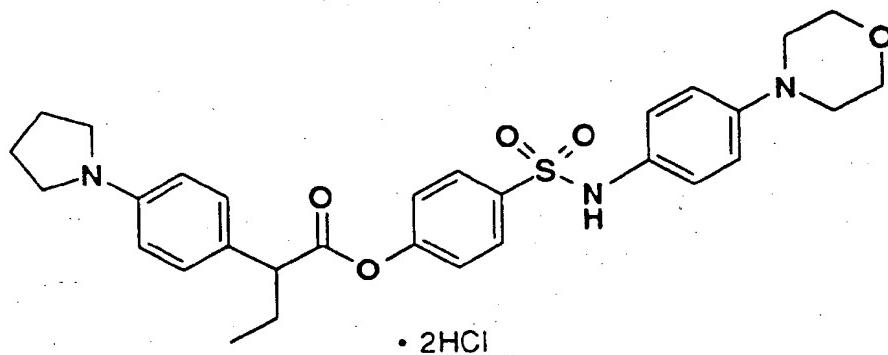
5 4-(N-(2-(tetrazol-5-yl)phenyl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



20 NMR (CDCl₃): δ 7.76 (1H, d, J=7.8Hz), 7.59 (1H, d, J=7.8Hz), 7.48 (1H, t-like), 7.35 (2H, d, J=8.8Hz), 7.26 (1H, t-like), 7.17 (2H, d, J=8.4Hz), 6.77 (2H, d, J=8.6Hz), 6.55 (2H, d, J=8.4Hz), 3.57 (1H, t, J=7.2Hz), 3.31-3.24 (4H, t-like), 2.25-1.75 (2H, m), 2.05-1.95 (4H, m), 0.97 (3H, t, J=7.2Hz);
 TLC : Rf 0.33 (acetic acid:methanol:chloroform=1:20:200).

25 Example 1(108)

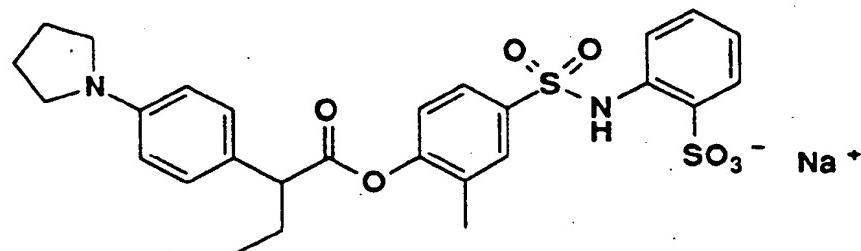
4-(N-4-(morpholin-4-yl)phenylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
 2hydrochloride



45 NMR (CD₃OD): δ 7.83 (2H, d, J=8.8Hz), 7.60 (4H, s), 7.55 (2H, d, J=9.0Hz), 7.29 (2H, d, J=9.0Hz), 7.16 (2H, d, J=8.8Hz), 4.05 (4H, t-like), 3.89 (1H, t, J=7.4Hz), 3.84-3.68 (4H, m), 3.58 (4H, t-like), 2.35-2.23 (4H, m), 2.30-2.09 and 2.04-1.78 (each 1H, m), 0.96 (3H, t, J=7.2Hz);
 TLC : Rf 0.52 (methanol:chloroform=1:20).

50 Example 1(109)

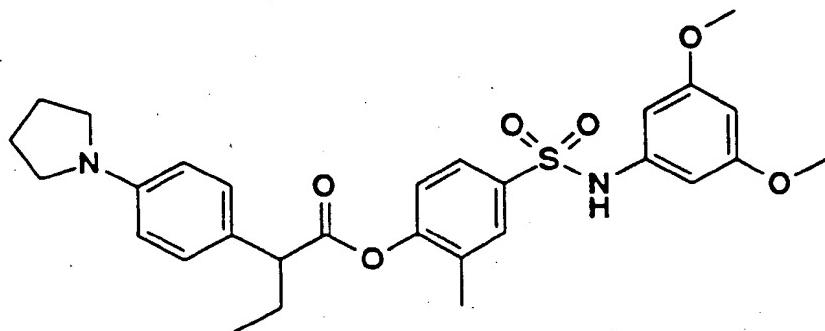
2-(N-(4-(2RS-(4-(pyrrolidin-1-yl)phenyl)butyloxy)-3-methylphenyl sulfonyl)amino)phenylsulfonic acid sodium salt



15 NMR (DMSO-d₆): δ 10.6 (1H, s), 7.81 (1H, d, J=2Hz), 7.71 (1H, dd, J=9,2Hz), 7.57 (1H, dd, J=8,2Hz), 7.37 (1H, dd, J=8,1Hz), 7.22 (1H, td, J=8,1Hz), 7.16 (2H, d, J=9Hz), 7.06 (1H, d, J=9Hz), 6.97 (1H, td, J=8,1Hz), 6.57 (2H, d, J=9Hz), 3.67 (1H, t, J=7Hz), 3.30-3.15 (4H, m), 2.18-1.90 (5H, m), 1.88 (3H, s), 1.87-1.65 (1H, m), 0.86 (3H, t, J=7Hz);
TLC : Rf 0.19 (chloroform:methanol:acetic acid=25:5:1).

Example 1(110)

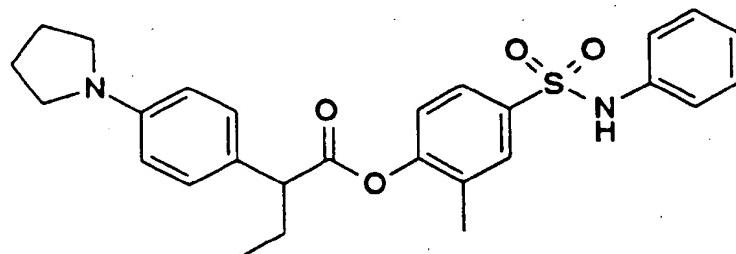
20 4-(N-3,5-dimethoxyphenylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



35 NMR (CDCl₃): δ 7.62-7.55 (2H, m), 7.18 (2H, d, J=8.4Hz), 6.98 (1H, d, J=8.2Hz), 6.69 (1H, s), 6.52 (2H, d, J=8.4Hz), 6.21-6.16 (3H, m), 3.69 (6H, s), 3.57 (1H, t, J=7.6Hz), 3.31-3.24 (4H, m), 2.25-1.80 (9H, m), 0.97 (3H, t, J=7.4Hz);
TLC : Rf 0.83 (hexane:ethyl acetate=1:1).

40 Example 1(111)

45 4-(N-phenylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

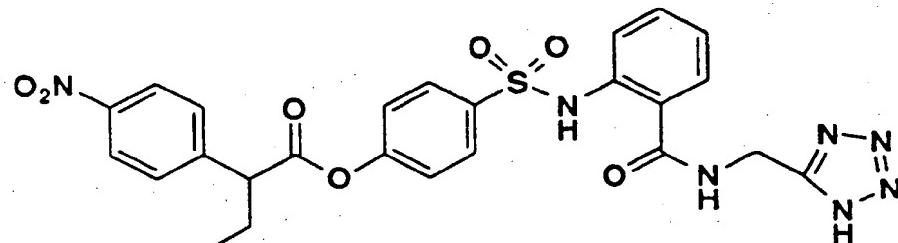


NMR (CDCl₃): δ 7.56-7.49 (2H, m), 7.26-6.94 (8H, m), 6.68 (1H, brs), 6.52 (2H, d, J=8.4Hz), 3.57 (1H, t, J=7.8Hz), 3.31-3.24 (4H, m), 2.27-1.75 (6H, m), 1.95 (3H, s), 0.97 (3H, t, J=7.4Hz);
TLC : Rf 0.83 (hexane:ethyl acetate=3:1).

Example 1(112)

4-(N-2-(N'-{(tetrazol-5-yl)methyl}carbamoyl)benzen-1-ylsulfamoyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester

5



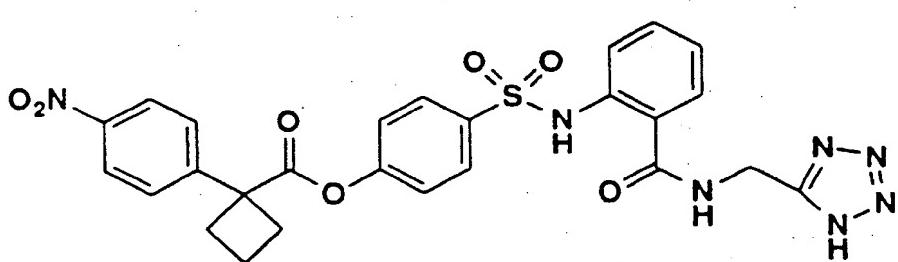
15

NMR (DMSO-d₆): δ 9.60-9.48 (1H, m), 8.25 (2H, d, J=8Hz), 7.88-7.63 (5H, m), 7.55-7.45 (2H, m), 7.30-7.09 (3H, m), 4.79-4.65 (2H, m), 4.13 (1H, t, J=7Hz), 2.31-2.04 (1H, m), 2.04-1.78 (1H, m), 0.88 (3H, t, J=7Hz);
TLC : Rf 0.28 (acetic acid:methanol:chloroform=1:2:30).

20 Example 1(113)

4-(N-2-(N'-{(tetrazol-5-yl)methyl}carbamoyl)benzen-1-ylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester

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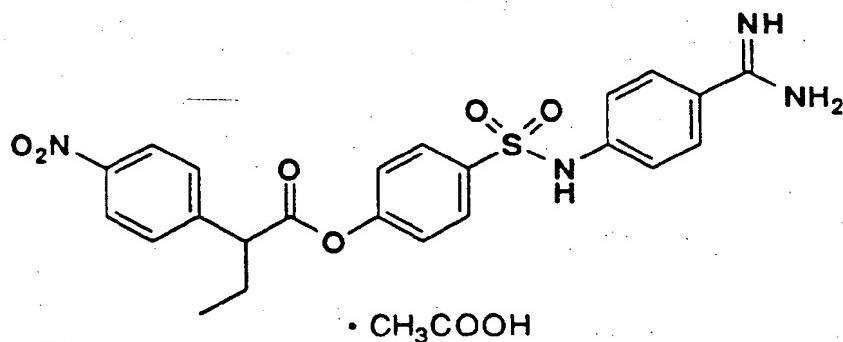
NMR (DMSO-d₆): δ 9.60-9.48 (1H, m), 8.33-8.20 (2H, m), 7.85-7.62 (5H, m), 7.55-7.40 (2H, m), 7.30-7.10 (3H, m), 4.78-4.65 (2H, m), 3.06-2.85 (2H, m), 2.75-2.55 (2H, m), 2.26-2.03 (1H, m), 2.03-1.80 (1H, m);
TLC : Rf 0.39 (acetic acid:methanol:chloroform=1:2:20).

40

Example 1(114)

4-(N-(4-amidinophenyl)sulfamoyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester · acetate

45



EP 0 769 498 A1

NMR (DMSO-d₆): δ 9.40-9.10 (2H, m), 8.75-8.55 (2H, m), 8.24 (2H, d, J=8Hz), 7.78-7.61 (4H, m), 7.44 (2H, d, J=8Hz), 7.05 (2H, d, J=8Hz), 6.83 (2H, d, J=8Hz), 4.09 (1H, t, J=7Hz), 2.23-2.00 (1H, m), 1.95-1.65 (4H, m), 0.88 (3H, t, J=7Hz);

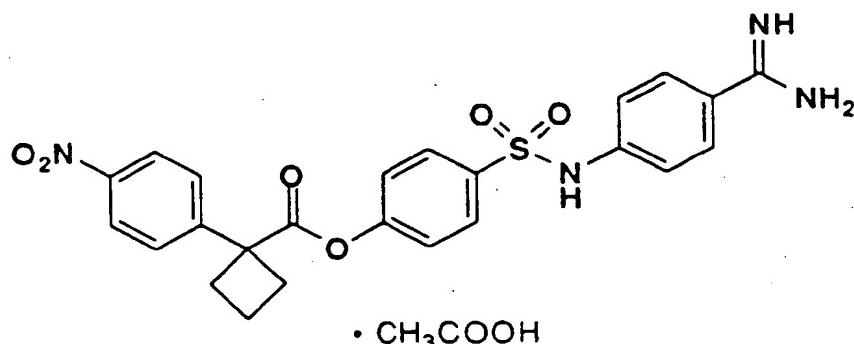
TLC : Rf 0.52 (acetic acid:methanol:chloroform=1:2:10).

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Example 1(115)

10 4-(N-(4-amidinophenyl)sulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester · acetate

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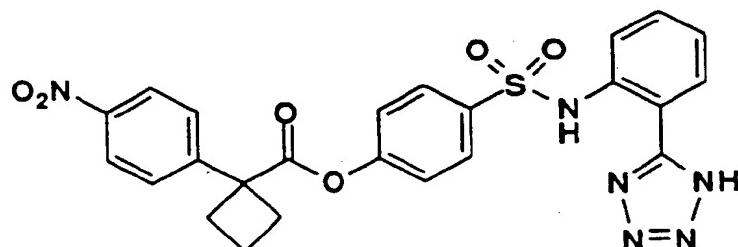


NMR (CD₃OD): δ 8.26 (2H, d, J=8Hz), 7.87 (2H, d, J=8Hz), 7.63 (4H, d, J=8Hz), 7.23 (2H, d, J=8Hz), 7.12 (2H, d, J=8Hz), 3.10-2.94 (2H, m), 2.78-2.60 (2H, m), 2.35-1.95 (5H, m);

TLC : Rf 0.40 (acetic acid:methanol:chloroform=1:2:15).

Example 1(116)

4-(N-2-(tetrazol-5-yl)phenylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester



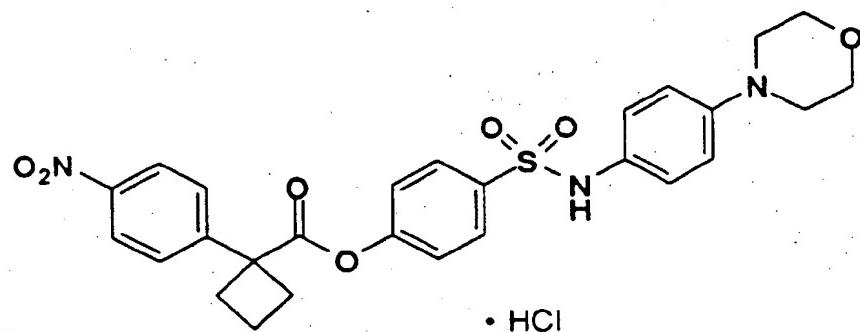
NMR (CD₃OD): δ 8.22 (2H, d, J=8.8Hz), 7.86-7.18 (8H, m), 6.96 (2H, d, J=8.8Hz), 3.08-2.88 (2H, m), 2.65 (2H, q-like), 2.28-2.08 (2H, m), 2.08-1.88 (2H, m);

TLC : Rf 0.43 (acetic acid:methanol:chloroform=1:3:30).

Example 1(117)

4-(N-4-(morpholin-4-yl)phenylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester · hydrochloride

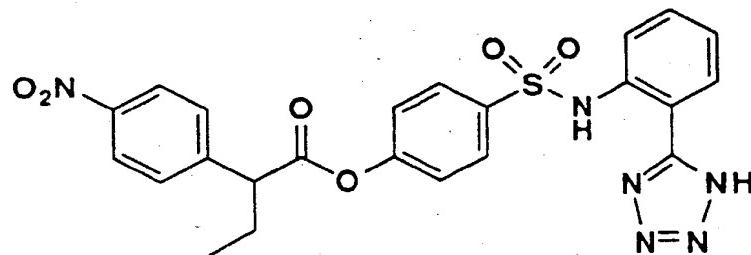
55



¹⁵ NMR (CD_3OD): δ 8.25 (2H, d, $J=8.8\text{Hz}$), 7.82 (2H, d, $J=8.8\text{Hz}$), 7.61 (2H, d, $J=8.8\text{Hz}$), 7.54 (2H, d, $J=8.8\text{Hz}$), 7.28 (2H, d, $J=8.8\text{Hz}$), 7.12 (2H, d, $J=8.8\text{Hz}$), 4.08 (4H, t, $J=4.8\text{Hz}$), 3.57 (4H, t, $J=4.8\text{Hz}$), 3.02 (2H, m), 2.70 (2H, m), 2.21 (1H, m), 2.03 (1H, m);
TLC: Rf 0.35 (hexane:ethyl acetate=1:1).

20 Example 1(118)

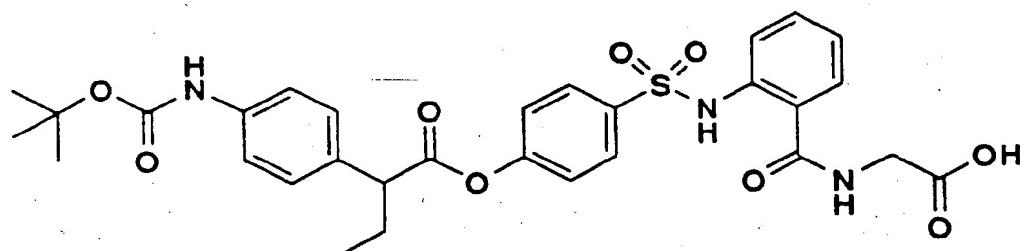
4-(N-2-(tetrazol-5-yl)phenylsulfamoyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester



³⁵ NMR (CD_3OD): δ 8.22 (2H, m), 7.93 (1H, d, $J=7.8\text{Hz}$), 7.68 (1H, d, $J=7.8\text{Hz}$), 7.64-7.60 (2H, t-like), 7.60-7.56 (2H, m), 7.33 (1H, t, $J=7.8\text{Hz}$), 7.16 (1H, t, $J=7.8\text{Hz}$), 7.00-6.92 (2H, m), 3.92 (1H, t, $J=8.0\text{Hz}$), 2.30-2.05 and 2.05-1.75 (each 1H, m), 0.93 (3H, t, $J=7.2\text{Hz}$);

Example 1(119)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(N-t-butyloxycarbonylamino)phenyl)butanoic acid ester



NMR (DMSO- d_6): δ 10.77 (1H, brs), 9.34 (1H, t-like), 7.82 (1H, d, $J=7\text{Hz}$), 7.79 (2H, d, $J=8\text{Hz}$), 7.44 (2H, d,

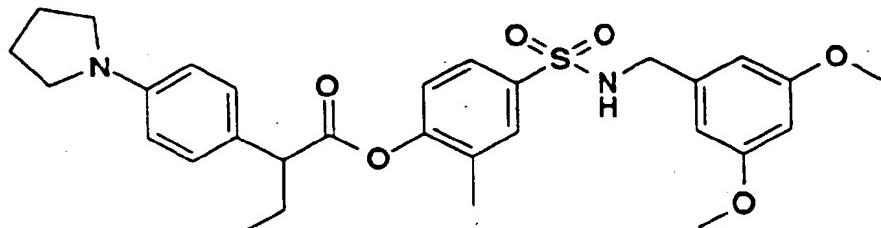
EP 0 769 498 A1

J=8Hz), 7.28-7.04 (7H, m), 6.78-6.70 (1H, m), 3.86 (2H, d-like), 3.72 (1H, t, J=7Hz), 2.11-1.90 and 1.81-1.67 (each 1H, m), 1.47 (9H, s), 0.87 (3H, t, J=7Hz);
 TLC : Rf 0.21 (chloroform:methanol:water=8:2:0.2).

5 Example 1(120)

4-(3,5-dimethoxybenzylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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15

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NMR (CDCl₃): δ7.67-7.62 (2H, m), 7.22 (2H, d, J=8.6Hz), 7.05 (1H, d, J=9.4Hz), 6.54 (2H, d, J=8.6Hz), 6.32 (3H, s), 4.64 (1H, t, J=6.0Hz), 4.05 (2H, d, J=6.0Hz), 3.72 (6H, s), 3.61 (1H, t, J=7.6Hz), 3.33-3.26 (4H, m), 2.27-1.81 (6H, m), 2.02 (3H, s), 0.99 (3H, t, J=7.2Hz);

TLC : Rf 0.86 (hexane:ethyl acetate=1:1).

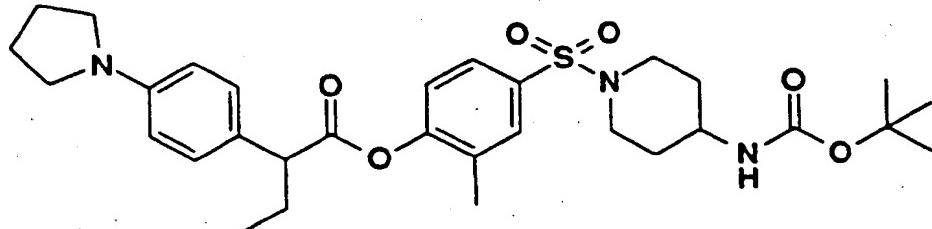
25

Example 1(121)

4-((4-t-butoxycarbonylaminopiperidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR (CDCl₃): δ7.55 (1H, s), 7.53 (1H, d, J=8.4Hz), 7.23 (2H, d, J=8.6Hz), 7.08 (1H, d, J=8.4Hz), 6.55 (2H, d, J=8.6Hz), 4.40 (1H, brs), 3.7-3.6 (2H, br), 3.62 (1H, t, J=7.7Hz), 3.5-3.2 (1H, br), 3.28 (4H, br), 2.6-2.4 (2H, m), 2.3-2.1 (1H, m), 2.04 (3H, s), 2.00 (4H, brs), 2.1-1.8 (1H, m), 1.6-1.4 (4H, m), 1.41 (9H, s), 0.99 (3H, t, J=7.3Hz);

45

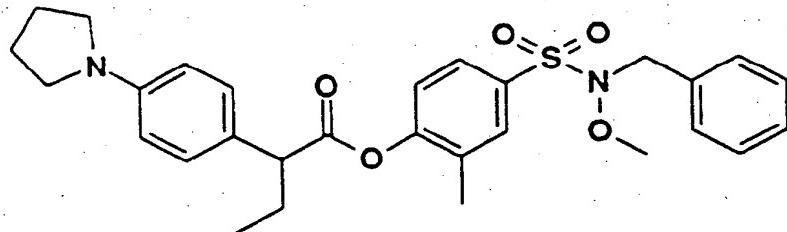
TLC : Rf 0.81 (hexane:ethyl acetate=1:1).

Example 1(122)

4-(N-methoxy-N-benzylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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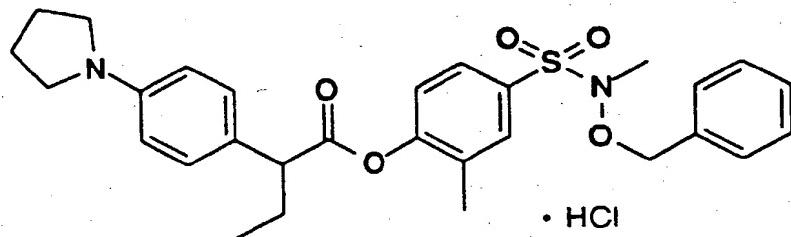


NMR (CDCl_3): δ 7.74 (1H, s), 7.72 (1H, d, $J=9.0\text{Hz}$), 7.32 (5H, s), 7.24 (2H, d, $J=8.8\text{Hz}$), 7.14 (1H, d, $J=9.0\text{Hz}$),
6.56 (2H, d, $J=8.8\text{Hz}$), 3.98 (2H, s), 3.64 (1H, t, $J=7.7\text{Hz}$), 3.43 (3H, s), 3.29 (4H, brs), 2.3-2.1 (1H, m), 2.08 (3H, s),
2.00 (4H, brs), 2.1-1.8 (1H, m), 1.00 (3H, t, $J=7.4\text{Hz}$);

15 TLC : Rf 0.79 (hexane:ethyl acetate=2:1).

Example 1(123)

20 4-(N-benzyloxy-N-methylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

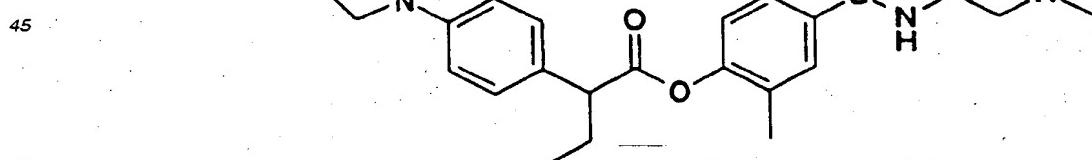


NMR (CDCl_3): δ 7.71 (1H, s), 7.68 (1H, d, $J=8.2\text{Hz}$), 7.5-7.2 (9H, brs), 7.09 (1H, d, $J=8.2\text{Hz}$), 5.00 (2H, s), 3.73
(1H, t, $J=7.5\text{Hz}$), 3.7-3.4 (4H, m), 2.65 (3H, s), 2.4-2.1 (5H, m), 2.03 (3H, s), 2.1-1.8 (1H, m), 0.99 (3H, t, $J=7.2\text{Hz}$);

35 TLC : Rf 0.66 (hexane:ethyl acetate=2:1).

Example 1(124)

40 4-(2-(N,N-dimethylamino)ethylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



NMR (CDCl_3): δ 7.69-7.63 (2H, m), 7.22 (2H, d, $J=8.6\text{Hz}$), 7.05 (1H, d, $J=8.4\text{Hz}$), 6.55 (2H, d, $J=8.6\text{Hz}$), 3.61
(1H, t, $J=8.2\text{Hz}$), 3.32-3.25 (4H, m), 2.95 (2H, t, $J=5.8\text{Hz}$), 2.30 (2H, t, $J=5.8\text{Hz}$), 2.27-1.65 (15H, m), 0.99 (3H, t,
 $J=7.2\text{Hz}$);

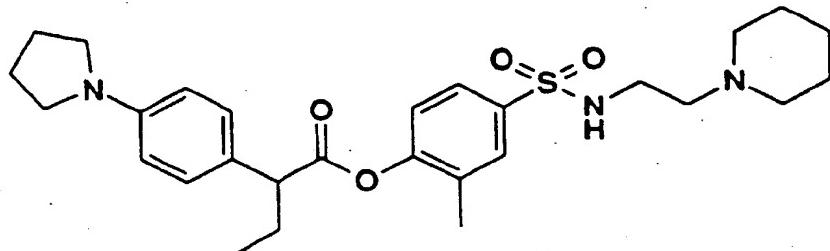
55 TLC : Rf 0.72 (chloroform:methanol:water=8:2:0.2).

Example 1(125)

4-(2-(piperidin-1-yl)ethylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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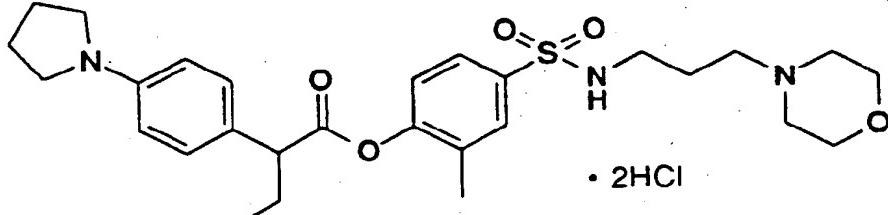
NMR (CDCl₃): δ 7.7-7.4 (m, 2H), 7.23 (d, J=8.7Hz, 2H), 7.05 (d, J=8.4Hz, 1H), 6.56 (d, J=8.7Hz, 2H), 3.61 (t, J=7.4Hz, 1H), 3.4-3.2 (m, 4H), 3.1-2.9 (m 2H), 2.5-2.4 (m, 2H), 2.4-2.3 (m, 4H), 2.3-1.8 (m, 2H), 2.1-1.9 (m, 4H), 2.03 (s, 3H), 1.6-1.3 (m, 6H), 0.99 (t, J=7.4Hz, 3H);

20 TLC : Rf 0.55 (chloroform:methanol=7:1).

Example 1(126)

4-(3-(morpholin-4-yl)propylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
25 hydrochloride

30



35

NMR (CDCl₃): δ 7.8-7.4 (m, 5H), 7.3-7.0 (m, 3H), 4.3-3.4 (m, 11H), 3.2-2.8 (m, 6H), 2.4-1.8 (m, 11H), 0.99 (t, J=7.2Hz, 3H);

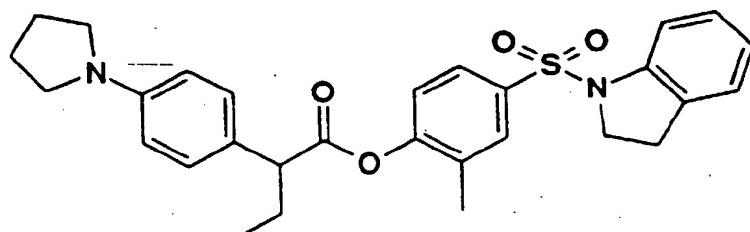
40 TLC : Rf 0.56 (chloroform:methanol=9:1).

Example 1(127)

4-(indolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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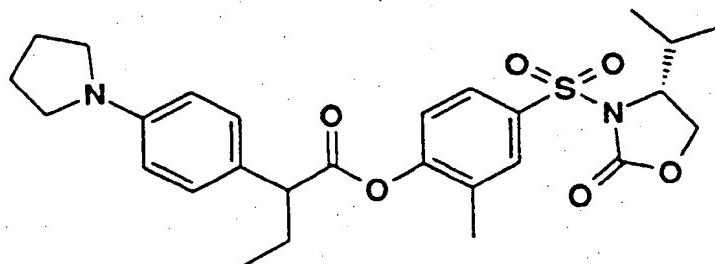
55

NMR (CDCl₃): δ 7.66-7.51 (3H, m), 7.24-6.88 (6H, m), 6.53 (2H, d, J=8.8Hz), 3.88 (2H, t, J=8.4Hz), 3.58 (1H, t, J=7.8Hz), 3.27 (4H, m), 2.89 (2H, t, J=8.4Hz), 2.29-1.72 (9H, m), 0.96 (3H, t, J=7.2Hz);

TLC : Rf 0.80 (hexane:ethyl acetate=1:1).

Example 1(128)

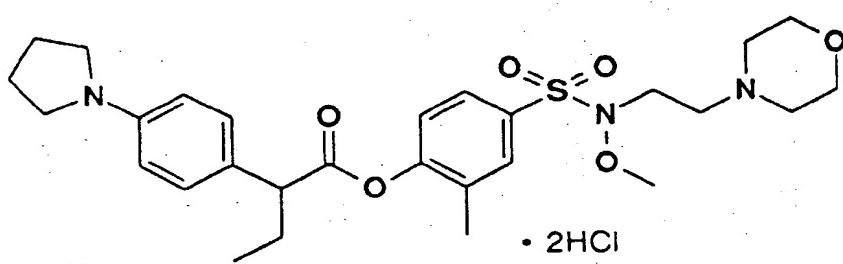
5 4-((2-oxo-4R-isopropylperhydroxazol-3-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



20 NMR (CDCl_3): 87.93 (1H, s), 7.86 (1H, d, $J=8.6\text{Hz}$), 7.22 (2H, d, $J=8.4\text{Hz}$), 7.11 (1H, d, $J=8.6\text{Hz}$), 6.55 (2H, d, $J=8.4\text{Hz}$), 4.43-4.33 (1H, m), 4.26 (1H, t, $J=8.6\text{Hz}$), 4.15 (1H, dd, $J=8.6, 3.2\text{Hz}$), 3.61 (1H, t, $J=7.7\text{Hz}$), 3.40-3.20 (4H, m), 2.55-2.33 (1H, m), 2.33-1.70 (9H, m), 0.99 (3H, t, $J=7.4\text{Hz}$), 0.91 (3H, d, $J=6.9\text{Hz}$), 0.76 (3H, d, $J=6.9\text{Hz}$);
TLC : Rf 0.43 (hexane:ethyl acetate=7:3).

25 Example 1(129)

30 4-(N-2-(morpholin-4-yl)ethyl-N-methoxyaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2 hydrochloride



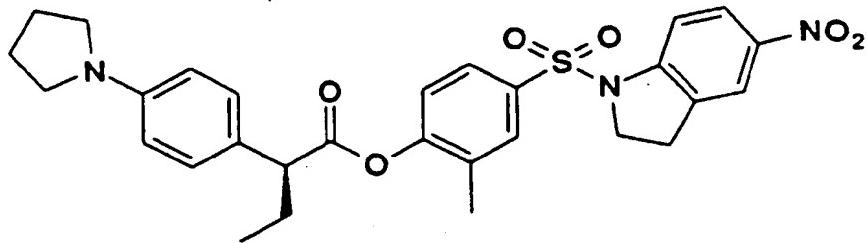
35 NMR (DMSO-d_6): 87.85-7.65 (2H, m), 7.27 (3H, d, $J=8.0\text{Hz}$), 6.95-6.70 (2H, brd), 4.05-3.70 (5H, m), 3.85 (3H, s), 3.50-2.95 (12H, m), 2.30-1.65 (6H, m), 2.02 (3H, s), 0.92 (3H, t, $J=7.5\text{Hz}$);
TLC : Rf 0.52 (hexane:ethyl acetate=2:1).

45 Example 1(130)

4-(5-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

50

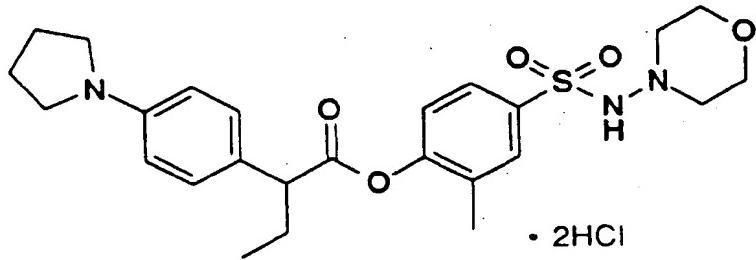
55



15 NMR (CDCl_3): δ 8.10 (1H, d, $J=9.0\text{Hz}$), 7.95 (1H, s), 7.72-7.56 (3H, m), 7.18 (2H, d, $J=8.0\text{Hz}$), 7.05 (1H, d, $J=8.0\text{Hz}$), 6.52 (2H, d, $J=8.0\text{Hz}$), 4.01 (2H, t, $J=8.5\text{Hz}$), 3.58 (1H, t, $J=7.5\text{Hz}$), 3.35-3.18 (4H, m), 3.08 (2H, t, $J=8.5\text{Hz}$), 2.30-1.70 (6H, m), 2.00 (3H, s), 0.96 (3H, t, $J=7.5\text{Hz}$);
TLC : Rf 0.60 (hexane:ethyl acetate=2:1).

20 Example 1(131)

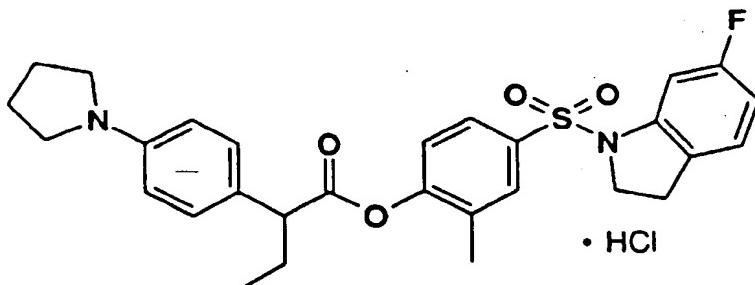
25 4-(morpholin-4-ylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
2hydrochloride



35 NMR (CD_3OD): δ 7.84-7.70 (2H, m), 7.64 (4H, s-like), 7.13 (1H, d, $J=8.2\text{Hz}$), 3.97 (1H, t, $J=7.4\text{Hz}$), 3.87-3.66 (4H, m), 3.54 (4H, t, $J=4.4\text{Hz}$), 2.55 (4H, t, $J=4.4\text{Hz}$), 2.43-2.14 (5H, m), 2.14-1.80 (4H, m), 1.00 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.51 (hexane:ethyl acetate=1:1).

40 Example 1(132)

45 4-(6-fluoroindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester - hydrochloride

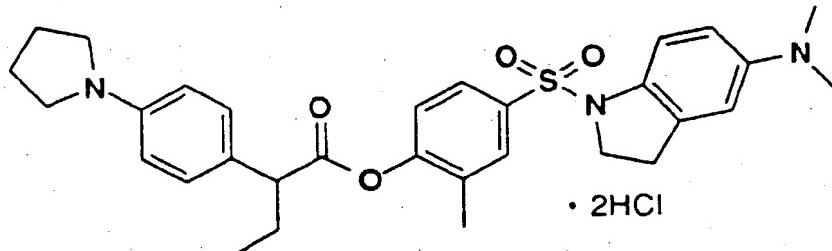


55 NMR ($\text{CD}_3\text{OD}:\text{CDCl}_3=1:1$): δ 7.75-7.40 (6H, m), 7.29 (1H, dd, $J=10.0$ and 2.0Hz), 7.15-7.01 (2H, m), 6.69 (1H, td, $J=8.6$ and 2.0Hz), 3.94 (2H, t, $J=8.4\text{Hz}$), 3.87 (1H, t, $J=7.6\text{Hz}$), 3.79-3.63 (4H, m), 2.89 (2H, t, $J=8.4\text{Hz}$), 2.40-2.12 (5H, m), 2.08-1.79 (4H, m), 0.99 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.29 (hexane:ethyl acetate=3:1).

Example 1(133)

4-(5-(N,N-dimethylamino)indolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2 hydrochloride

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NMR (CD_3OD): δ 7.78-7.64 (3H, m), 7.60 (4H, s-like), 7.52-7.42 (2H, m), 7.11 (1H, d, $J=8.4\text{Hz}$), 4.01 (2H, t, $J=8.5\text{Hz}$), 3.93 (1H, t, $J=8.4\text{Hz}$), 3.87-3.70 (4H, m), 3.23 (6H, s), 3.06 (2H, t, $J=8.5\text{Hz}$), 2.40-2.10 (5H, m), 2.10-1.80 (4H, m), 0.97 (3H, t, $J=7.2\text{Hz}$);

TLC : Rf 0.24 (hexane : ethyl acetate = 3:1).

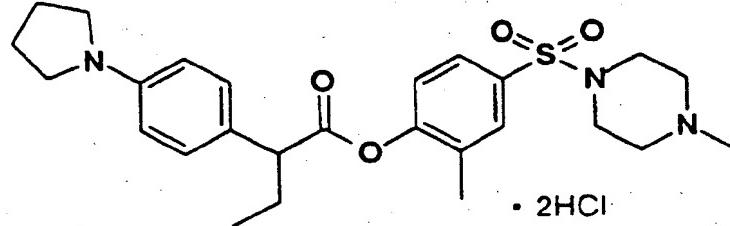
20

Example 1(134)

4-(4-methylpiperazin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2 hydrochloride

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NMR (CD_3OD): δ 7.75-7.59 (6H, m), 7.23 (1H, d, $J=8.2\text{Hz}$), 4.06-3.84 (3H, m), 3.84-3.68 (4H, m), 3.64-3.49 (2H, m), 3.32-3.11 (2H, m), 2.89 (3H, s), 2.84-2.64 (2H, m), 2.44-2.14 (5H, m), 2.13-1.82 (4H, m), 1.00 (3H, t, $J=7.2\text{Hz}$);

TLC : Rf 0.36 (ethyl acetate).

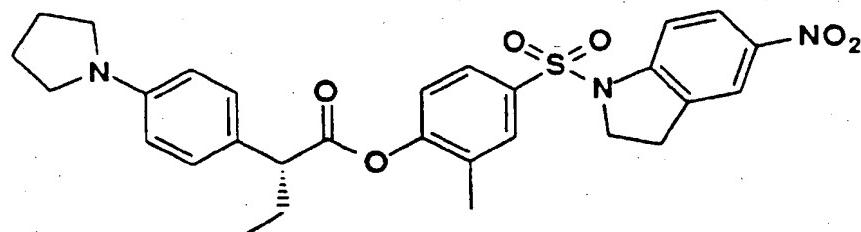
45

Example 1(135)

4-(5-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR (CDCl_3): δ 8.10 (1H, dd, $J=9.0, 2.2\text{Hz}$), 7.95 (1H, d, $J=2.2\text{Hz}$), 7.66 (1H, d, $J=9.0\text{Hz}$), 7.66 (1H, s), 7.63 (1H,

d, J=8.2Hz), 7.18 (2H, d, J=8.8Hz), 7.05 (1H, d, J=8.2Hz), 6.53 (2H, d, J=8.8Hz), 4.01 (2H, t, J=8.5Hz), 3.58 (1H, t, J=7.7Hz), 3.3-3.2 (4H, brs), 3.08 (2H, t, J=8.5Hz), 2.3-2.0 (1H, m), 2.1-1.9 (4H, brs), 2.00 (3H, s), 2.0-1.8 (1H, m), 0.96 (3H, t, J=7.3Hz);

TLC : Rf 0.60 (hexane:ethyl acetate=2:1).

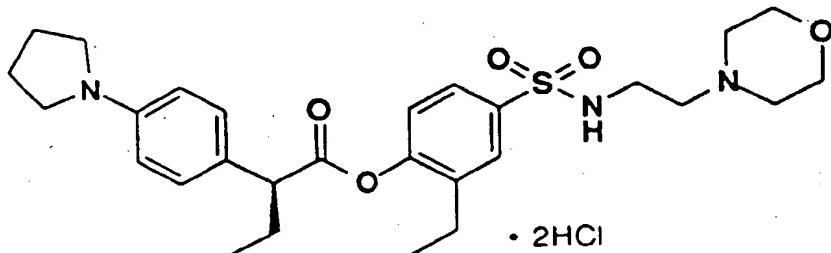
5

Example 1(136)

4-(2-(morpholin-4-yl)ethylaminosulfonyl)-2-ethylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
2hydrochloride

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NMR (CD_3OD): δ7.83-7.58 (6H, m), 7.18 (1H, d, J=8.0Hz), 4.12-3.70 (9H, m), 3.53 (2H, d, J=12.0Hz), 3.38-3.08 (6H, m), 2.45-1.80 (8H, m), 1.00 (6H, t, J=7.5Hz);

25

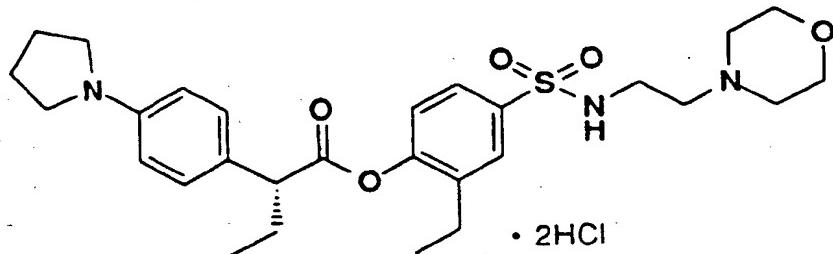
TLC : Rf 0.41 (hexane:ethyl acetate=1:4).

Example 1(137)

4-(2-(morpholin-4-yl)ethylaminosulfonyl)-2-ethylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
2hydrochloride

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NMR (CD_3OD): δ7.83-7.58 (6H, m), 7.19 (1H, d, J=8.0Hz), 4.12-3.70 (9H, m), 3.53 (2H, d, J=12.0Hz), 3.40-3.08 (6H, m), 2.50-1.80 (8H, m), 0.99 (6H, t, J=7.5Hz);

45

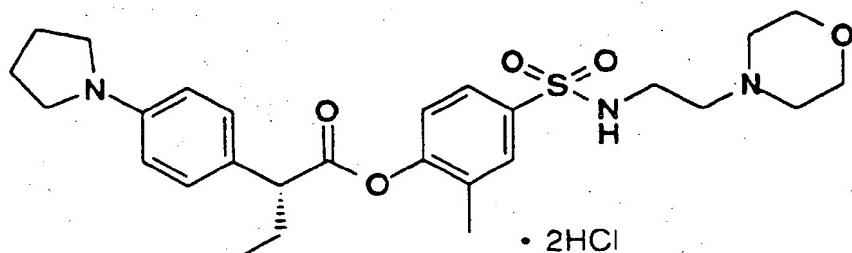
TLC : Rf 0.41 (hexane:ethyl acetate=1:4).

Example 1(138)

4-(2-(morpholin-4-yl)ethylaminosulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
2hydrochloride

50

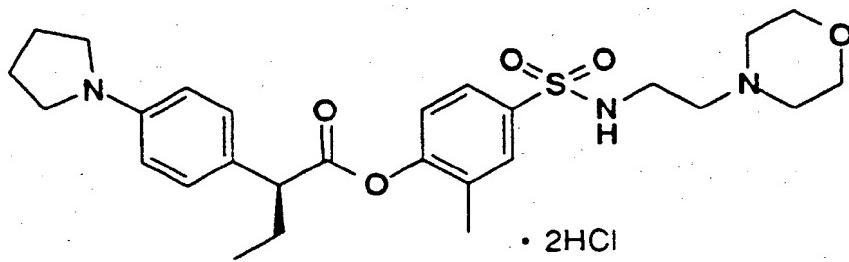
55



15 NMR (DMSO-d₆): δ11.0-10.8 (1H, brs), 7.75 (1H, s), 7.70 (1H, d, J=8.6Hz), 7.22 (2H, d, J=8.4Hz), 7.18 (1H, d, J=8.6Hz), 6.64 (2H, d, J=8.4Hz), 4.0-3.7 (5H, m), 3.4-3.0 (12H, m), 2.2-2.0 (1H, m), 2.1-1.9 (4H, brs), 2.0-1.7 (1H, m), 1.97 (3H, s), 0.91 (3H, t, J=7.3Hz);
TLC : Rf 0.50 (chloroform:methanol=9:1).

Example 1(139)

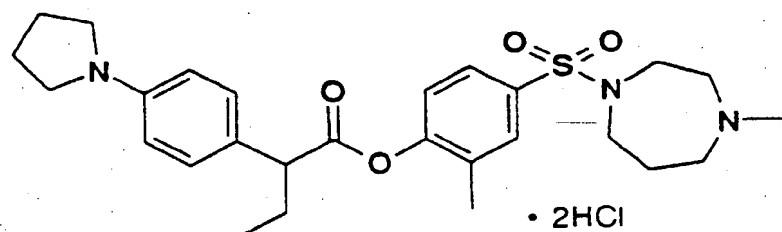
20 4-(2-(morpholin-4-yl)ethylaminosulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride



35 NMR (DMSO-d₆): δ11.4-11.2 (1H, brs), 7.76 (1H, s), 7.70 (1H, d, J=8.6Hz), 7.30 (2H, d, J=8.4Hz), 7.18 (1H, d, J=8.6Hz), 6.87 (2H, d, J=8.4Hz), 4.0-3.7 (5H, m), 3.5-3.3 (6H, m), 3.3-3.0 (6H, m), 2.2-2.0 (1H, m), 2.1-1.9 (4H, brs), 2.0-1.7 (1H, m), 1.98 (3H, s), 0.91 (3H, t, J=7.2Hz);
TLC : Rf 0.50 (chloroform:methanol=9:1).

40 Example 1(140)

45 4-(4-methyl-1,4-perhydrodiazepin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

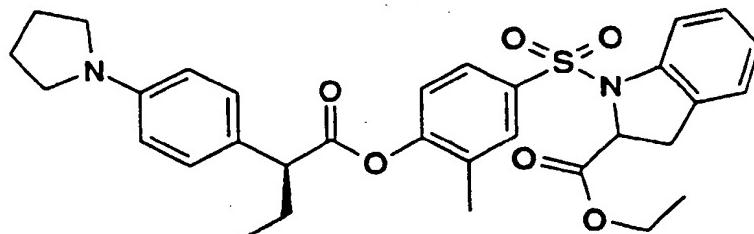


NMR (DMSO-d₆): δ7.72 (1H, d, J=2Hz), 7.66 (1H, dd, J=2 and 8Hz), 7.25 (2H, d, J=8Hz), 7.19 (1H, d, J=8Hz), 6.76 (2H, d-like), 3.76 (1H, t, J=7Hz), 3.75-3.01 (12H, m), 2.76 and 2.74 (total 3H, each s), 2.21-1.66 (8H, m), 1.99 (3H, s), 0.91 (3H, t, J=7Hz);

TLC : Rf 0.52 (chloroform:methanol:water=9:1:0.1).

Example 1(141)

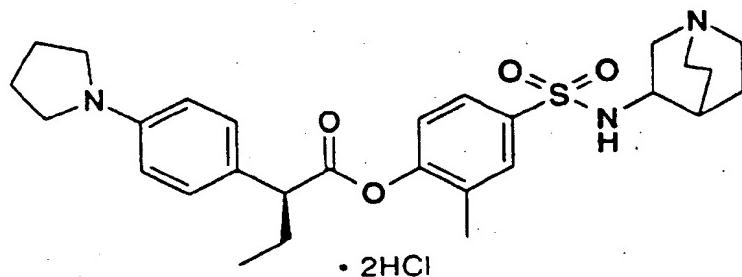
- 5 4-(2RS-ethoxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



²⁰ NMR (CDCl_3): δ 7.62-7.51 (3H, m), 7.23-7.15 (3H, m), 7.07-6.95 (3H, m), 6.52 (2H, d, $J=9\text{Hz}$), 4.75-4.67 (1H, m), 4.24 (2H, q, $J=7\text{Hz}$), 3.57 (1H, t, $J=7\text{Hz}$), 3.31-3.24 (4H, m), 3.21-3.00 (2H, m), 2.23-1.75 (2H, m), 2.04-1.99 (4H, m), 1.96 (3H, s), 1.29 (3H, t, $J=7\text{Hz}$), 0.96 (3H, t, $J=7\text{Hz}$);
TLC: Rf 0.29 (hexane:ethyl acetate=3:1).

Example 1(142)

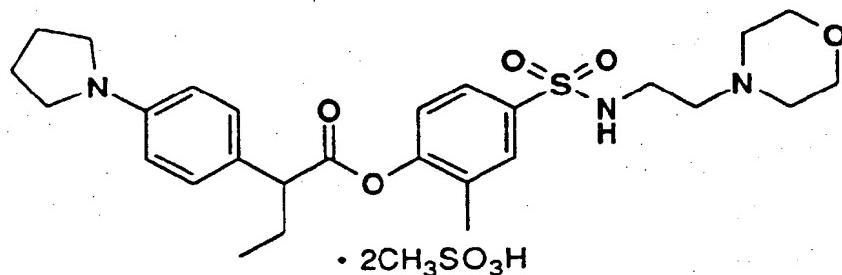
- 25 4-(quinuclidin-3RS-ylaminosulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
2hydrochloride



40 NMR (DMSO-d₆): δ8.35 (1H, d, J=7Hz), 7.74-7.64 (2H, m), 7.26 (2H, d, J=8Hz), 7.17 (1H, d, J=8Hz), 6.82-6.70 (2H, br), 3.75 (1H, t, J=7Hz), 3.61-3.43 (1H, br), 3.40-3.22 (5H, m), 3.18-2.94 (5H, m), 2.90-2.79 (1H, m), 2.17-1.60 (13H, m), 0.91 (3H, t, J=7Hz);
TLC : Rf 0.35 (chloroform:methanol:water=8:2:0.2).

Example 1(143)

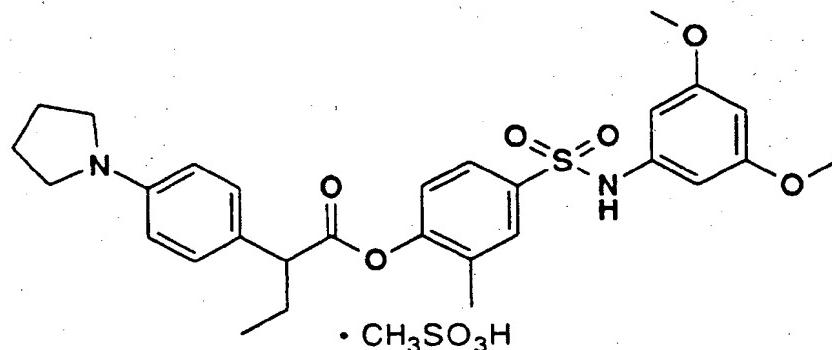
- 4-(2-(morpholin-4-yl)ethylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
2methanesulfonic acid salt



15 NMR (CD₃OD): δ7.80-7.70 (2H, m), 7.67 (4H, s), 7.17 (1H, d, J=8.0Hz), 4.10-3.70 (9H, m), 3.54 (2H, d, J=12.0Hz),
3.40-3.10 (6H, m), 2.70 (6H, s), 2.40-1.80 (6H, m), 2.05 (3H, s), 1.00 (3H, t, J=7.5Hz);
TLC : R_f 0.31 (chloroform:methanol:acetic acid=40:2:1).

Example 1(144)

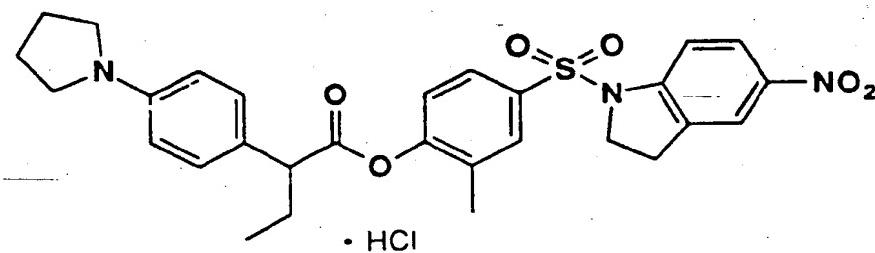
20 4-(3,5-dimethoxyphenylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · methanesulfonic acid salt



35 NMR (CD₃OD): δ7.70-7.50 (6H, m), 7.05 (1H, d, J=8.5Hz), 6.24 (2H, d, J=2.0Hz), 6.16 (1H, t, J=2.0Hz), 3.94 (1H, t, J=7.5Hz), 3.77 (4H, t-like), 3.67 (6H, s), 2.70 (3H, s), 2.40-1.80 (6H, m), 1.96 (3H, s), 0.98 (3H, t, J=7.5Hz);
TLC : R_f 0.73 (hexane:ethyl acetate=1:1).

Example 1(145)

40 4-(5-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



55 NMR (CDCl₃): δ8.11 (1H, dd, J=2.0, 9.0Hz), 7.96 (1H, d, J=2.0Hz), 7.72-7.60 (3H, m), 7.55 (2H, d, J=8.0Hz),
7.44 (2H, d, J=8.0Hz), 7.06 (1H, d, J=8.0Hz), 4.03 (2H, t, J=8.5Hz), 3.75 (1H, t, J=7.5Hz), 3.85-3.40 (4H, m), 3.10 (2H,

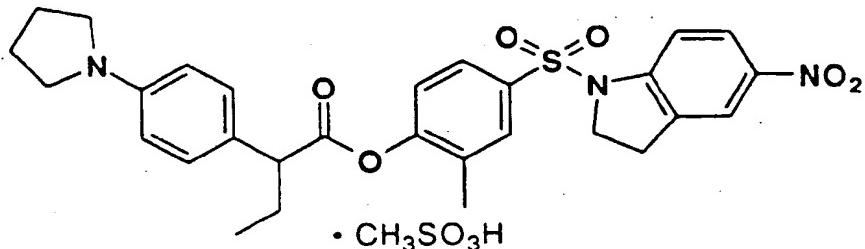
EP 0 769 498 A1

t, J=8.5Hz), 2.45-2.20 (4H, m), 2.40-1.75 (2H, m), 2.02 (3H, s), 0.98 (3H, t, J=7.5Hz);
 TLC : Rf 0.60 (hexane:ethyl acetate=2:1).

Example 1(146)

5 4-(5-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · methanesulfonic acid salt

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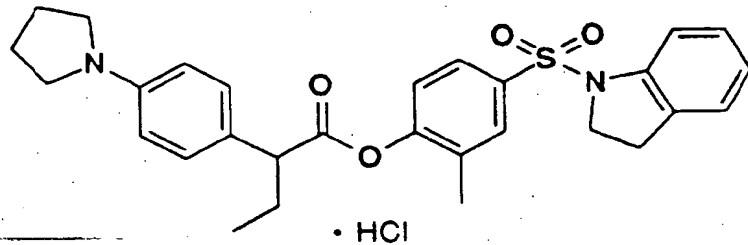
NMR (CDCl₃): 88.11 (1H, dd, J=2.5, 9.0Hz), 7.97 (1H, d, J=2.5Hz), 7.74-7.62 (3H, m), 7.57 (2H, d, J=8.5Hz),
 7.49 (2H, d, J=8.5Hz), 7.07 (1H, d, J=8.0Hz), 4.03 (2H, t, J=8.5Hz), 3.77 (1H, t, J=7.5Hz), 4.10-3.30 (4H, m), 3.11 (2H,
 t, J=8.5Hz) 2.85 (3H, s), 2.50-2.20 (4H, m), 2.40-2.10 and 2.10-1.80 (each 1H, m), 2.04 (3H, s), 0.99 (3H, t, J=7.5Hz);
 TLC : Rf 0.60 (hexane:ethyl acetate=2:1).

25

Example 1(147)

4-(indolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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NMR (CDCl₃): 87.65-7.53 (3H, m), 7.32 (2H, d, J=8.4Hz), 7.24-6.90 (6H, m), 3.89 (2H, t, J=8.5Hz), 3.66 (1H, t,
 J=8.2Hz), 3.45 (4H, brs), 2.89 (2H, t, J=8.5Hz), 2.34-2.04 (5H, m), 1.97 (3H, s), 2.04-1.73 (1H, m), 0.97 (3H, t, J=7.2Hz);
 TLC : Rf 0.42 (hexane:ethyl acetate=3:1).

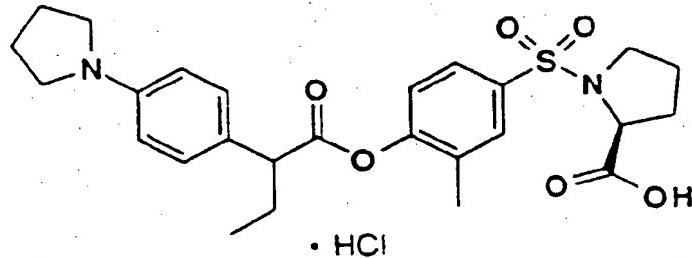
45

Example 2

4-(2S-carboxypyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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To a mixture solution of the compound prepared in example 1 (1.04 g) in dichloromethane(5 ml) and anisole (5 ml) were slowly added trifluoroacetic acid (5 ml) at 0 °C. The reaction mixture was stirred for 6h at room temperature. The reaction mixture was concentrated, and the residue was purified by column chromatography on silica gel (chloroform:methanol=20:1) to give N-[4-[2RS-(4-(1-pyrrolidinyl)phenyl]butyloxy]-3-methylphenyl sulfonyl]-L-proline. The obtained above compound was converted to hydrochloride salt by the following method. To a solution of N-[4-[2RS-(4-(1-pyrrolidinyl)phenyl]butyloxy]-3-methylphenyl sulfonyl]-L-proline in dioxane (5 ml) was added 4N hydrochloric acid in dioxane solution (1 ml) at 0 °C. The reaction mixture was stirred for 5 min, and reaction mixture was concentrated to give the title compound (1 g) having the following physical data.

NMR (CDCl_3): δ 7.70 (1H, s), 7.67 (1H, d, $J=8.0\text{Hz}$), 7.59 (2H, d, $J=8.5\text{Hz}$), 7.49 (2H, d, $J=8.5\text{Hz}$), 7.07 (1H, d, $J=8.0\text{Hz}$), 4.26 (1H, dd, $J=3.5, 7.0\text{Hz}$), 3.78 (1H, t, $J=7.5\text{Hz}$), 3.75-3.60 (4H, m), 3.52-3.40 (1H, m), 3.33-3.14 (1H, m), 2.40-2.25 (4H, m), 2.40-1.65 (6H, m), 2.04 (3H, s), 1.00 (3H, t, $J=7.5\text{Hz}$);

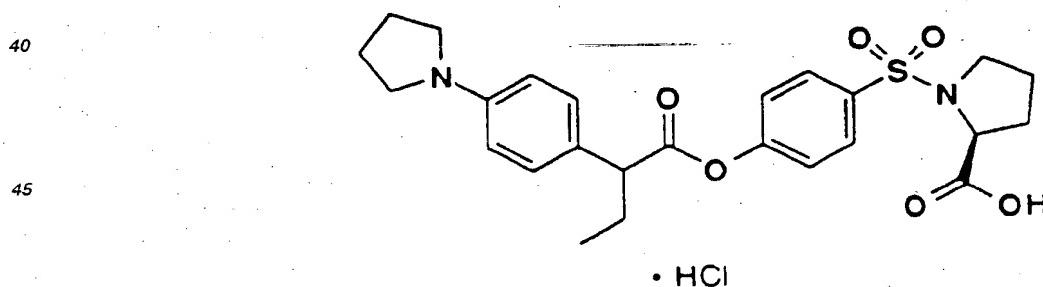
25 TLC : Rf 0.39 (acetic acid:methanol:chloroform=1:2:40).

Example 2(1)~2(296)

By the same procedure as example 1 and example 2 and by known method converted to corresponding salts, acid addition salts or solvates, the compounds having the following physical data were given by using corresponding phenol derivatives instead of the compound prepared in reference example 4 and by using corresponding carboxylic acid derivatives instead of the compound prepared in reference example 7.

Example 2(1)

35 4-(2S-carboxypyrrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

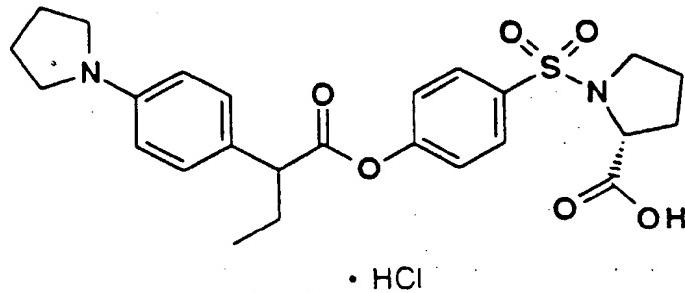


50 NMR(DMSO-d_6): δ 7.86 (2H, d, $J=8\text{Hz}$), 7.24 (4H, d, $J=8\text{Hz}$), 6.78 (2H, d, $J=8\text{Hz}$), 4.15-4.05 (1H, m), 3.73 (1H, t, $J=7\text{Hz}$), 3.40-3.05 (6H, m), 2.20-1.45 (10H, m), 0.89 (3H, t, $J=7\text{Hz}$);

TLC : Rf 0.26 (acetic acid:methanol:chloroform=1:2:60).

55 Example 2(2)

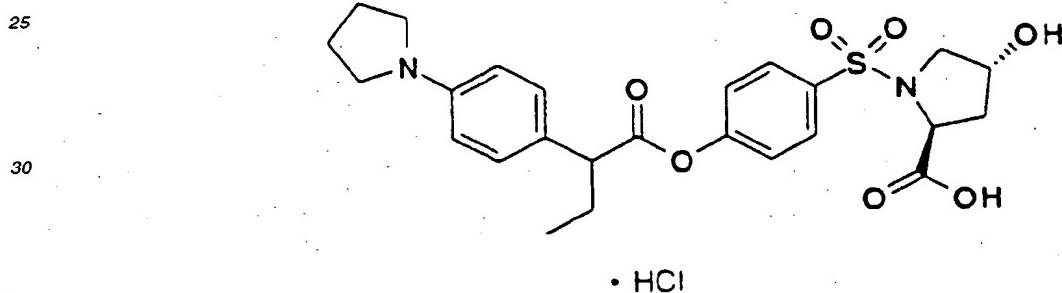
4-(2R-carboxypyrrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



15 NMR (DMSO-d₆): δ 7.86 (2H, d, J=8.8Hz), 7.25 (4H, d, J=8.8Hz), 6.78 (2H, d, J=8.8Hz), 4.16-4.05 (1H, m), 3.74
 (1H, t, J=7.2Hz), 3.44-3.06 (2H, m), 3.36-3.24 (4H, m), 2.22-1.46 (10H, m), 0.90 (3H, t, J=7.2Hz);
 TLC : Rf 0.39 (acetic acid:methanol:chloroform=1:2:40).

Example 2(3)

20 4-(2S-carboxy-4R-hydroxypyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



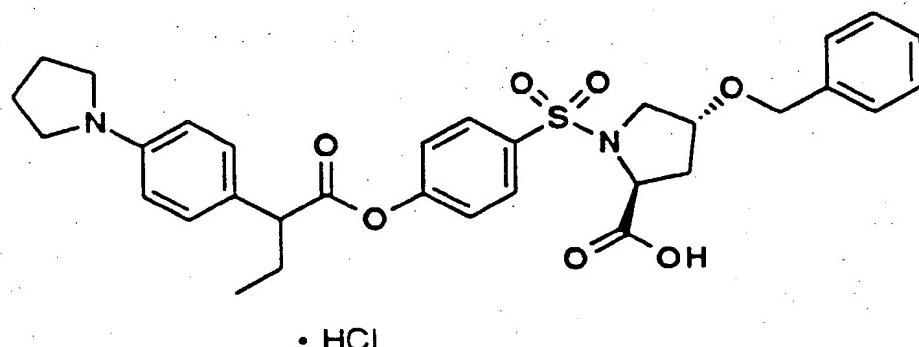
40 NMR (DMSO-d₆): δ 7.83 (2H, d, J=9Hz), 7.31-7.18 (4H, m), 6.85-6.68 (2H, m), 4.25-4.14 (1H, m), 4.04 (1H, t, J=7Hz), 3.73 (1H, t, J=7Hz), 3.50-3.38 (5H, m), 3.18-3.05 (1H, m), 2.20-1.65 (8H, m), 0.90 (3H, t, J=7Hz);
 TLC : Rf 0.27 (chloroform:methanol:acetic acid=20:2:1).

Example 2(4)

45 4-(2S-carboxy-4R-benzyloxyprrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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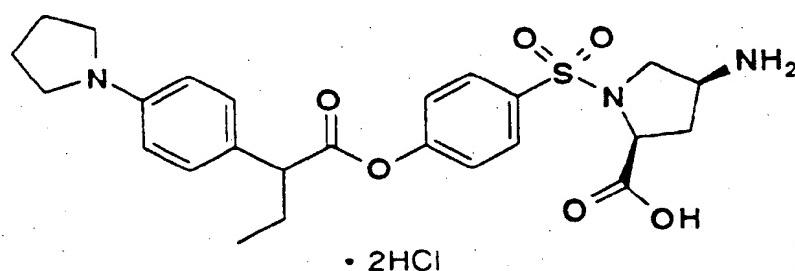


NMR (CDCl_3): δ 7.84 (2H, d, $J=9\text{Hz}$), 7.62 (2H, d, $J=9\text{Hz}$), 7.47 (2H, d, $J=9\text{Hz}$), 7.34-7.19 (3H, m), 7.17-7.00 (4H, m), 4.30 (1H, t, $J=8\text{Hz}$), 4.23 (2H, s), 4.15-4.03 (1H, m), 3.86-3.42 (7H, m), 2.47-2.05 (7H, m), 2.05-1.74 (1H, m), 0.97 (3H, t, $J=7\text{Hz}$);

TLC : Rf 0.35 (chloroform:methanol:acetic acid=40:2:1).

Example 2(5)

4-(2S-carboxy-4S-aminopyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
2hydrochloride

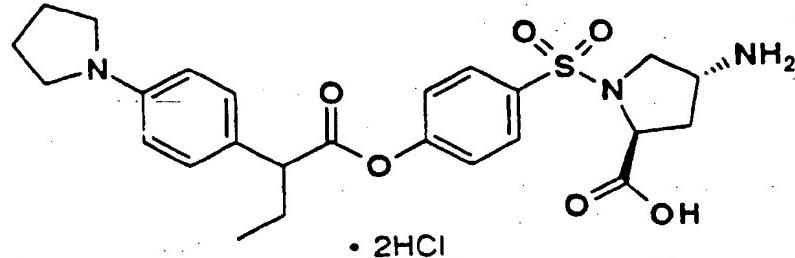


NMR (DMSO-d₆): δ 8.55-8.20 (2H, brs), 7.89 (2H, d, J=9Hz), 7.29 (2H, d, J=9Hz), 7.25 (2H, d, J=9Hz), 6.73 (2H, d, J=9Hz), 5.80-4.40 (1H, m), 4.18 (1H, t, J=7Hz), 3.74 (1H, t, J=7Hz), 3.64-3.10 (7H, m), 2.67-2.40 (1H, m), 2.20-1.65 (7H, m), 0.90 (3H, t, J=7Hz);

TLC : Rf 0.49 (ethyl acetate:acetic acid:water=6:2:1).

Example 2(6)

45 4-(2S-carboxy-4R-aminopyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
2hydrochloride



EP 0 769 498 A1

NMR (DMSO-d₆): δ 8.60-8.30 (2H, brs), 7.88 (2H, d, J=9Hz), 7.28 (2H, d, J=9Hz), 7.23 (2H, d, J=9Hz), 6.72 (2H, d, J=9Hz), 5.40-4.20 (1H, m), 4.40 (1H, dd, J=9Hz, 4Hz), 3.90-3.50 (2H, m), 3.50-3.10 (6H, m), 2.33-1.60 (8H, m), 0.90 (3H, t, J=7Hz);

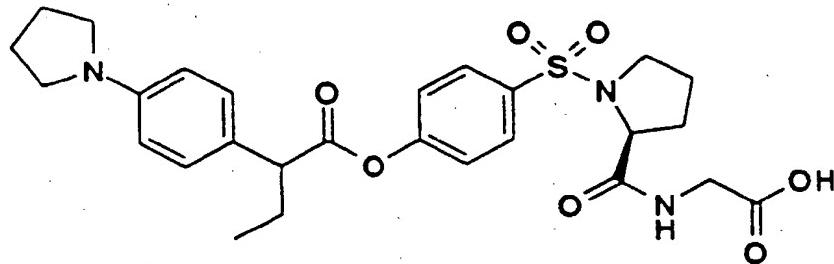
TLC : Rf 0.42 (ethyl acetate:acetic acid:water=6:2:1).

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Example 2(7)

10 4-(2S-(N-carboxymethylcarbamoyl)pyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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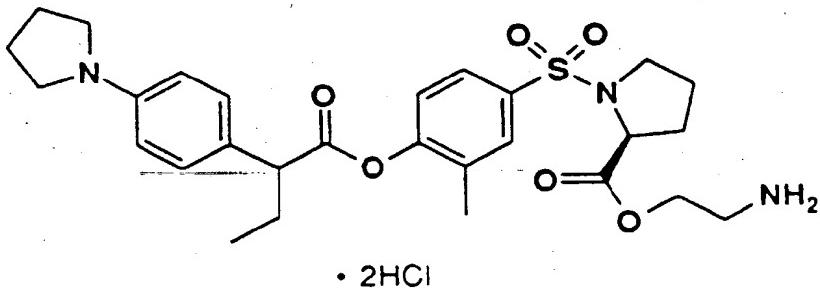
25 NMR (CDCl₃+CD₃OD): δ 7.84 (2H, d, J=8.8Hz), 7.28-7.18 (4H, m), 6.72 (2H, d, J=8.8Hz), 4.09-3.85 (3H, m), 3.71-3.53 (2H, m), 3.41-3.31 (4H, m), 3.20-3.08 (1H, m), 2.26-1.59 (10H, m), 0.99 (3H, t, J=7.4Hz);

TLC : Rf 0.24 (chloroform:methanol:acetic acid=40:2:1).

Example 2(8)

30 4-(2S-(2-aminoethoxycarbonyl)pyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

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40

· 2HCl

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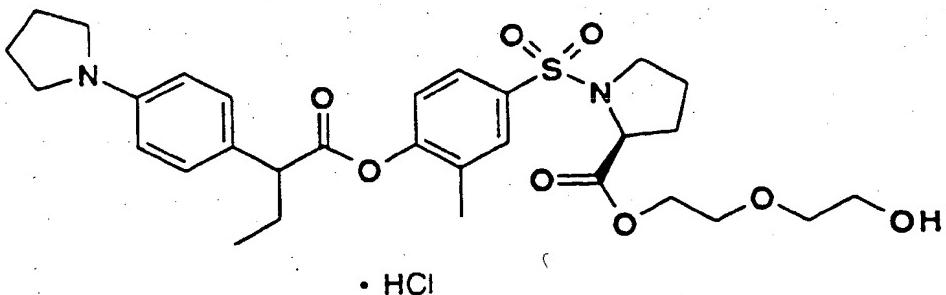
NMR (DMSO-d₆): δ 8.21 (2H, brs), 7.75 (1H, s), 7.69 (1H, d, J=8.2Hz), 7.22 (3H, m), 6.70 (2H, d, J=8.8Hz), 4.26 (3H, m), 3.50-3.36 (2H, m), 3.31 (4H, m), 3.20 (1H, m), 3.08 (2H, m), 2.12 (1H, m), 2.00 (3H, s), 1.96 (4H, m), 1.87 (4H, m), 1.66 (1H, m), 0.92 (3H, t, J=7.2Hz);

TLC : Rf 0.31 (chloroform:methanol:acetic acid=12:1:1).

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Example 2(9)

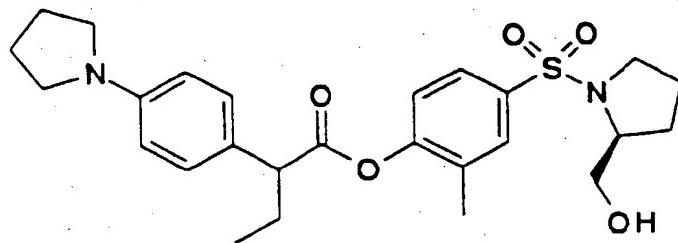
55 4-(2S-(2-(2-hydroxyethoxy)ethoxycarbonyl)pyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



15 NMR (CDCl_3): δ 7.69 (1H, s), 7.67 (2H, d, $J=8.4\text{Hz}$), 7.23 (2H, d, $J=8.4\text{Hz}$), 7.07 (1H, d, $J=8.2\text{Hz}$), 6.56 (2H, d, $J=8.4\text{Hz}$), 4.29 (3H, m), 3.75-3.58 (7H, m), 3.50 (1H, m), 3.29 (4H, m), 3.22 (1H, m), 2.16 (1H, m), 2.04 (3H, s), 2.01 (4H, m), 1.98-1.64 (5H, m), 0.99 (3H, t, $J=7.2\text{Hz}$);
TLC : Rf 0.62 (chloroform:methanol=9:1).

20 Example 2(10)

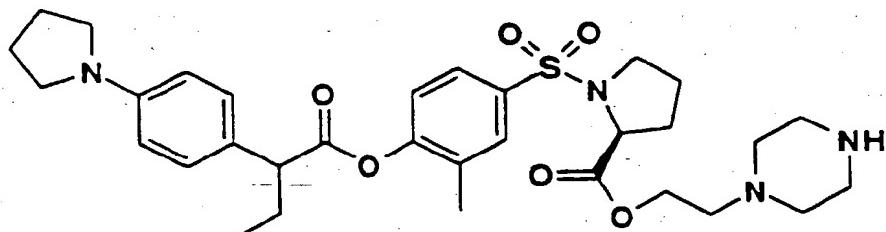
4-(2S-hydroxymethylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



35 NMR (CDCl_3): δ 7.70-7.58 (2H, m), 7.22 (2H, d, $J=8.5\text{Hz}$), 7.09 (1H, d, $J=8.0\text{Hz}$), 6.55 (2H, d, $J=8.5\text{Hz}$), 3.80-3.52 (3H, m), 3.62 (1H, t, $J=7.5\text{Hz}$), 3.52-3.35 (1H, m), 3.35-3.12 (5H, m), 2.90-2.55 (1H, brs), 2.35-1.70 (2H, m), 2.05 (3H, s), 2.05-1.95 (4H, m), 1.80-1.30 (4H, m), 0.99 (3H, t, $J=7.5\text{Hz}$);
TLC : Rf 0.36 (hexane:ethyl acetate=1:1).

40 Example 2(11)

4-(2S-(2-(piperazin-4-yl)ethyl)oxycarbonylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride



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NMR (CD_3OD): δ 7.82-7.63 (6H, m), 7.00 (1H, d, $J=8.2\text{Hz}$), 4.62 (2H, m), 4.41 (1H, m), 4.00 (1H, t, $J=7.6\text{Hz}$),

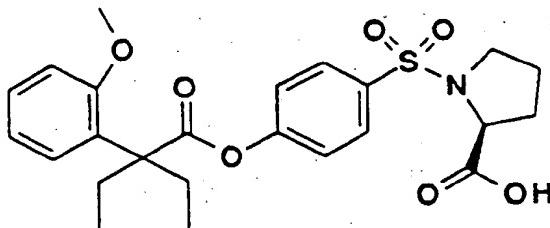
EP 0 769 498 A1

3.81-3.66 (8H, m), 3.57 (1H, m), 3.21 (1H, ml, 2.33 (7H, m), 2.07 (3H, s), 2.03-1.89 (5H, m), 1.69 (1H, m), 1.00(3H, t, J=7.4Hz);

TLC : Rf 0.48 (chloroform:methanol:water=40:10:1).

5 Example 2(12)

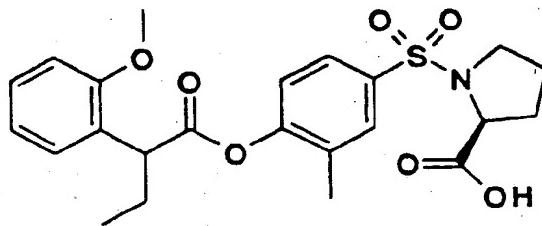
4-(2S-carboxypyrrolidin-1-ylsulfonyl)phenyl 2-(2-methoxyphenyl)-2-ethylbutanoic acid ester



20 NMR (DMSO-d₆): δ 7.89 (2H, d, J=9Hz), 7.34-7.16 (4H, m), 7.06-6.95 (2H, m), 4.03 (1H, dd, J=2 and 8Hz), 3.82 (3H, s), 3.36-3.23 and 3.20-3.09 (each 1H, m), 2.23-1.91 (4H, m), 1.87-1.47 (4H, m), 0.72 (6H, t, J=7Hz);
TLC : Rf 0.19 (chloroform:methanol:water=9:1:0.1).

Example 2(13)

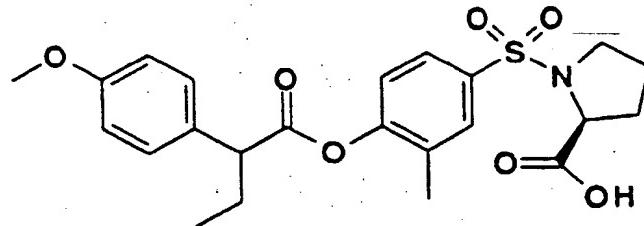
25 4-(2S-carboxypyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(2-methoxyphenyl)butanoic acid ester



30 NMR (CDCl₃): δ 7.69 (1H, s), 7.68 (1H, d, J=9.0Hz), 7.35-7.22 (2H, m), 7.10 (1H, d, J=9.0Hz), 6.98 (1H, d, J=7.6Hz), 6.92 (1H, d, J=7.8Hz), 4.28-4.16 (1H, m), 4.15 (1H, t, J=7.6Hz), 3.85 (3H, s), 3.60-3.43 (1H, m), 3.26-3.07 (1H, m), 2.35-1.56 (4H, m), 2.04 (3H, s), 0.98 (3H, t, J=7.6Hz);
TLC : Rf 0.54 (chloroform:methanol:water=8:2:0.2).

Example 2(14)

45 4-(2S-carboxypyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester



NMR (DMSO-d₆): δ 7.74 (1H, s), 7.69 (1H, d, J=8.2Hz), 7.33 (2H, d, J=8.8Hz), 7.17 (1H, d, J=8.2Hz), 6.95 (2H,

EP 0 769 498 A1

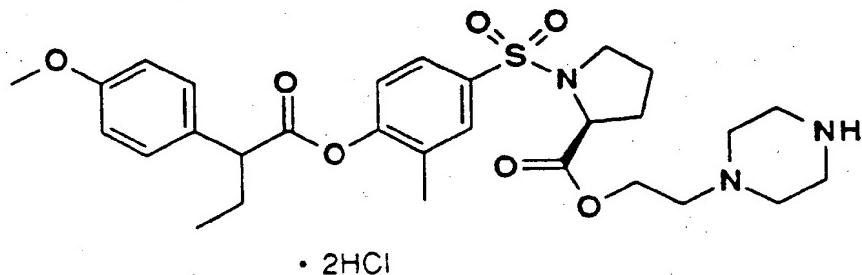
d, J=8.8Hz), 4.11 (1H, m), 4.14 (1H, m), 3.76 (3H, s), 3.30 (1H, m), 3.17 (1H, m), 2.10 (1H, m), 1.96 (3H, s), 1.82 (4H, m), 1.56 (1H, m), 0.91 (3H, t, J=7.2Hz);

TLC : Rf 0.58 (chloroform:methanol:acetic acid=12:1:1).

5 Example 2(15)

4-(2S-(2-(piperazin-1-yl)ethyl)oxycarbonylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester · 2hydrochloride

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NMR (CD_3OD): δ 7.77 (1H, s), 7.75 (1H, d, J=7.4Hz), 7.32 (2H, d, J=8.6Hz), 7.16 (1H, d, J=7.4Hz), 6.93 (2H, d, J=8.6Hz), 4.62 (2H, brs), 4.5-4.3 (1H, br), 3.8-3.4 (12H, br), 3.79 (3H, s), 3.3-3.1 (1H, br), 2.3-1.8 (6H, br), 2.00 (3H, s), 0.98 (3H, t, J=7.3Hz);

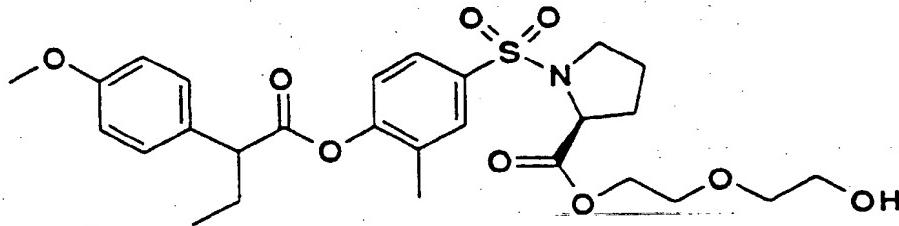
25 TLC : Rf 0.16 (chloroform:methanol:acetic acid=40:2:1).

Example 2(16)

4-(2S-(2-(2-hydroxyethoxy)ethoxycarbonyl)pyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester

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40



45 NMR (CDCl_3): δ 7.70 (1H, s), 7.68 (1H, d, J=8.8Hz), 7.31 (2H, d, J=8.4Hz), 7.01 (1H, d, J=8.8Hz), 6.90 (2H, d, J=8.4Hz), 4.3-4.2 (3H, m), 3.82 (3H, s), 3.8-3.7 (6H, m), 3.7-3.5 (2H, m), 3.3-3.2 (1H, m), 2.4-2.1 (2H, m), 2.00 (3H, s), 2.1-1.7 (4H, m), 0.99 (3H, t, J=7.3Hz);

TLC : Rf 0.24 (hexane:ethyl acetate=1:2).

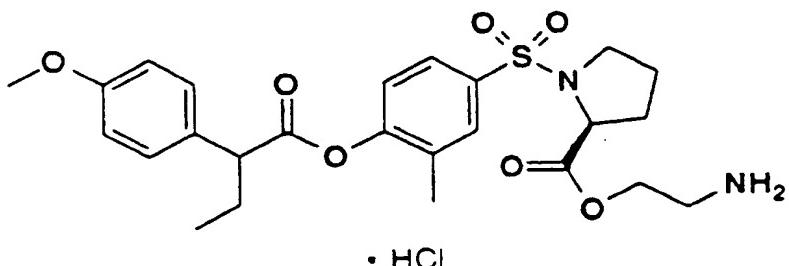
Example 2(17)

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4-(2S-(2-aminoethyl)oxycarbonylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester · hydrochloride

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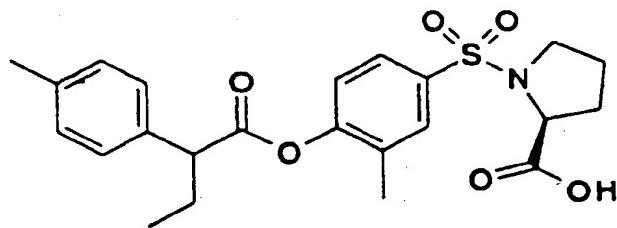
10

NMR (CDCl_3): δ 8.40 (2H, brs), 7.73 (1H, s), 7.70 (1H, d, $J=9.2\text{Hz}$), 7.30 (2H, d, $J=8.6\text{Hz}$), 7.08 (1H, d, $J=9.2\text{Hz}$),
 6.89 (2H, d, $J=8.6\text{Hz}$), 4.6-4.3 (3H, br), 3.80 (3H, s), 3.67 (1H, t, $J=7.6\text{Hz}$), 3.6-3.3 (3H, br), 3.2-3.1 (1H, br), 2.4-1.8
 (6H, brj, 2.00 (3H, s), 0.98 (3H, t, $J=7.3\text{Hz}$);
 TLC : Rf 0.23 (chloroform:methanol=9:1).

Example 2(18)

20 4-(2S-carboxypyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester

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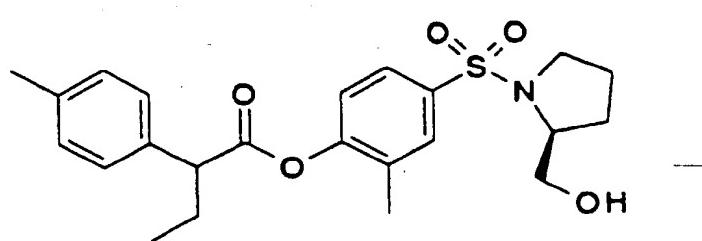
NMR (CDCl_3): δ 7.69 (1H, s), 7.66 (1H, d, $J=9.0\text{Hz}$), 7.25 (2H, d, $J=8.0\text{Hz}$), 7.15 (2H, d, $J=8.0\text{Hz}$), 7.05 (1H, d,
 J=9.0Hz), 4.20 (1H, m), 3.67 (1H, t, $J=8.0\text{Hz}$), 3.60-3.40 (1H, m), 3.20-3.00 (1H, m), 2.34 (3H, s), 2.30-1.50 (6H, m),
 1.96 (3H, s), 0.97 (3H, t, $J=7.5\text{Hz}$);
 TLC : Rf 0.39 (acetic acid:methanol:chloroform=1:2:40).

Example 2(19)

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4-(2S-hydroxymethylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester

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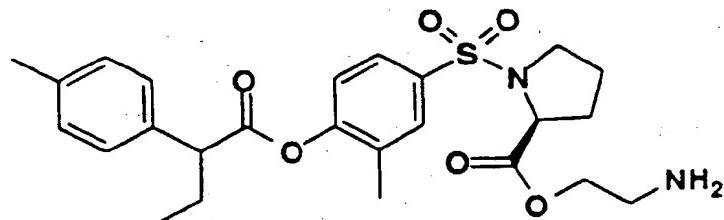
NMR (CDCl_3): δ 7.67 (1H, s), 7.65 (1H, d, $J=8.0\text{Hz}$), 7.28 (2H, d, $J=8.0\text{Hz}$), 7.18 (2H, d, $J=8.0\text{Hz}$), 7.09 (1H, d,
 J=8.0Hz), 3.70 (1H, t, $J=7.5\text{Hz}$), 3.74-3.54 (3H, m), 3.54-3.38 (1H, m), 3.30-3.14 (1H, m), 2.71 (1H, t-like), 2.36 (3H,
 s), 2.40-1.80 (2H, m), 2.02 (3H, s), 1.90-1.60 (3H, m), 1.60-1.40 (1H, m), 1.00 (3H, t, $J=7.5\text{Hz}$);
 TLC : Rf 0.23 (ethyl acetate:hexane=1:2).

Example 2(20)

4-(2S-(2-aminoethyl)oxycarbonylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester
· hydrochloride

5

10



15

• HCl

NMR (DMSO-d₆): δ 8.22 (3H, brs), 7.75 (1H, d, J=1.8Hz), 7.70 (1H, dd, J=8.4 and 1.8Hz), 7.30 (2H, d, J=8.0Hz),
20 7.20 (3H, d, J=8.0Hz), 4.33-4.15 (1H, m), 4.26 (2H, t, J=5.0Hz), 3.85 (1H, t, J=7.6Hz), 3.49-3.01 (2H, m), 3.09 (2H, t,
J=5.6Hz), 2.32 (3H, s), 2.25-1.50 (6H, m), 1.98 (3H, s), 0.92 (3H, t, J=7.2Hz);
TLC : Rf 0.56 (chloroform:methanol:acetic acid=15:2:1).

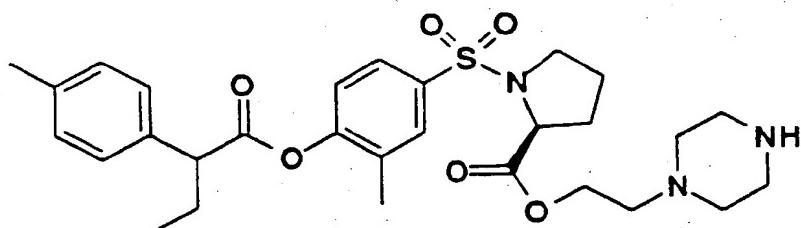
Example 2(21)

25

4-(2S-(2-(piperazin-4-yl)ethyl)oxycarbonylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic
acid ester · 2hydrochloride

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35



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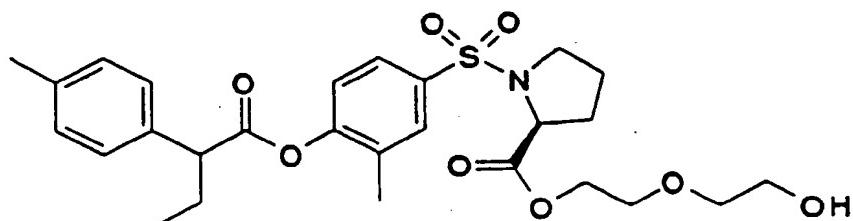
• 2HCl

NMR (CD₃OD): δ 7.78 (1H, s), 7.75 (1H, dd, J=8.6 and 1.2Hz), 7.29 (2H, d, J=8.0Hz), 7.24-7.12 (3H, m), 4.66-4.54
45 (2H, m), 4.45-4.32 (1H, m), 3.85-3.60 (11H, m), 3.60-3.38 (1H, m), 3.26-3.15 (1H, m), 2.34 (3H, s), 2.30-1.55 (6H, m),
1.99 (3H, s), 0.98 (3H, t, J=7.2Hz);
TLC : Rf 0.45 (chloroform:methanol:water=8:2:0.2).

Example 2(22)

50 4-(2S-(2-(2-hydroxyethoxy)ethyl)oxycarbonylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)buta-
noic acid ester

55

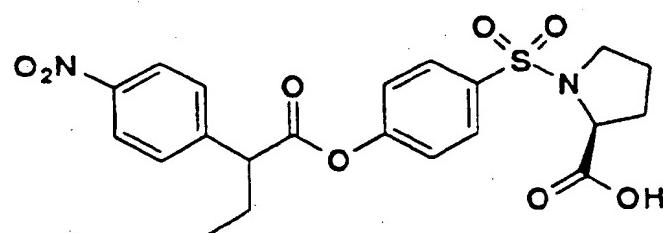


NMR (CDCl_3): δ 7.70 (1H, s), 7.68 (1H, dd, $J=7.4$ and 2.4Hz), 7.28 (2H, d, $J=8.2\text{Hz}$), 7.18 (2H, d, $J=8.2\text{Hz}$), 7.07 (1H, d, $J=8.8\text{Hz}$), 4.40-4.20 (3H, m), 3.73-3.37 (8H, m), 3.37-3.16 (1H, m), 2.24-1.63 (6H, m), 2.36 (3H, s), 2.02 (3H, s), 1.70 (1H, s), 1.00 (3H, t, $J=7.2\text{Hz}$);

15 TLC : Rf 0.28 (ethyl acetate:hexane=2:1).

Example 2(23)

20 4-(2S-carboxypyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester

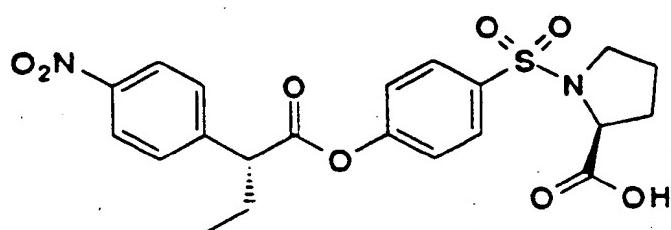


NMR (DMSO-d_6): δ 8.25 (2H, d, $J=8\text{Hz}$), 7.90 (2H, d, $J=8\text{Hz}$), 7.58 (2H, d, $J=8\text{Hz}$), 7.19 (2H, d, $J=8\text{Hz}$), 5.70-4.80 (1H, brs), 4.30 (1H, dd, $J=7\text{Hz}$, 4Hz), 3.85 (1H, t, $J=7\text{Hz}$), 3.60-3.39 (1H, m), 3.39-3.15 (1H, m), 2.45-1.65 (6H, m), 1.01 (3H, t, $J=7\text{Hz}$);

35 TLC : Rf 0.34 (acetic acid:methanol:chloroform=1:2:40).

Example 2(24)

40 4-(2S-carboxypyrrolidin-1-ylsulfonyl)phenyl 2R-(4-nitrophenyl)butanoic acid ester

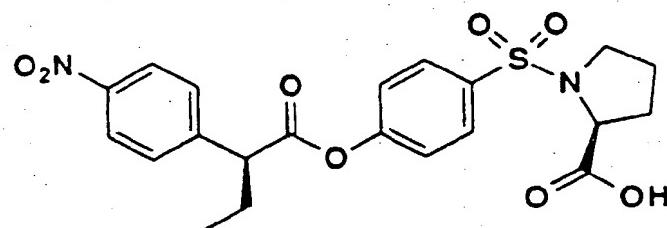


NMR (CDCl_3): δ 8.26 (d, $J=8.8\text{Hz}$, 2H), 7.90 (d, $J=8.8\text{Hz}$, 2H), 7.58 (d, $J=8.8\text{Hz}$, 2H), 7.20 (d, $J=8.8\text{Hz}$, 2H), 4.30 (dd, $J=4.0$, 7.8Hz , 1H), 3.86 (t, $J=7.6\text{Hz}$, 1H), 3.5-3.4 (m, 1H), 3.4-3.2 (m, 1H), 2.4-1.7 (m, 6H), 1.02 (t, $J=7.3\text{Hz}$, 3H);

55 TLC : Rf 0.63 (chloroform:methanol=6:1).

Example 2(25)

4-(2S-carboxypyrrolidin-1-ylsulfonyl)phenyl 2S-(4-nitrophenyl)butanoic acid ester



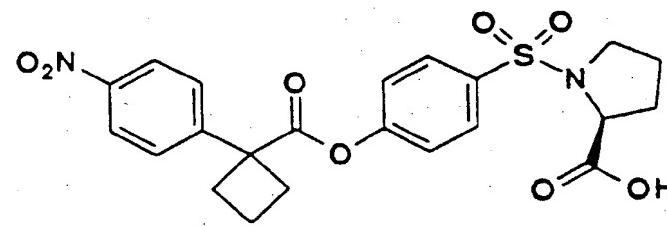
NMR (CDCl_3): δ 8.26 (d, $J=8.8\text{Hz}$, 2H), 7.90 (d, $J=8.8\text{Hz}$, 2H), 7.58 (d, $J=8.8\text{Hz}$, 2H), 7.19 (d, $J=8.8\text{Hz}$, 2H), 4.31 (dd, $J=4.0, 7.2\text{Hz}$, 1H), 3.86 (t, $J=7.7\text{Hz}$, 1H), 3.6-3.4 (m, 1H), 3.4-3.2 (m, 1H), 2.4-1.7 (m, 6H), 1.03 (t, $J=7.6\text{Hz}$, 3H);
TLC : Rf 0.63 (chloroform:methanol=6:1).

15

Example 2(26)

4-(2S-carboxypyrrolidin-1-ylsulfonyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester

20



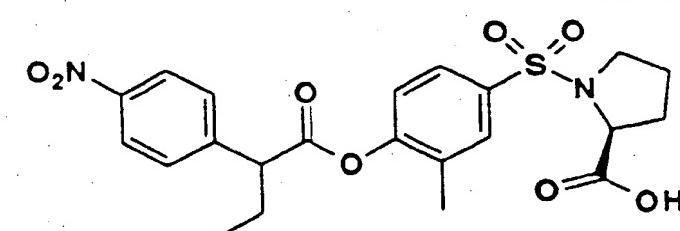
NMR (DMSO-d_6): δ 8.27 (2H, d, $J=8\text{Hz}$), 7.88 (2H, d, $J=8\text{Hz}$), 7.56 (2H, d, $J=8\text{Hz}$), 7.16 (2H, d, $J=8\text{Hz}$), 6.00-5.10 (1H, brs), 4.29 (1H, dd, $J=7\text{Hz}, 4\text{Hz}$), 3.55-3.40 (1H, m), 3.34-3.19 (1H, m), 3.15-2.98 (2H, m), 2.80-2.60 (2H, m), 2.38-1.66 (6H, m);
TLC : Rf 0.40 (acetic acid:methanol:chloroform=1:2:40).

35

Example 2(27)

4-(2S-carboxypyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester

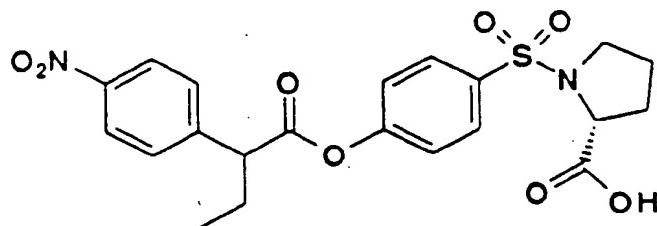
40



NMR (DMSO-d_6): δ 8.27 (2H, d, $J=8.8\text{Hz}$), 7.74 (2H, d, $J=8.8\text{Hz}$), 7.79-7.66 (2H, m), 7.23 (1H, d, $J=8.4\text{Hz}$), 4.20 (1H, t, $J=7.6\text{Hz}$), 4.12-4.06 (1H, m), 3.40-3.07 (2H, m), 2.35-1.40 (6H, m), 2.00 (3H, s), 0.92 (3H, t, $J=7.2\text{Hz}$);
TLC : Rf 0.19 (acetic acid:methanol:chloroform=1:2:40).

55 Example 2(28)

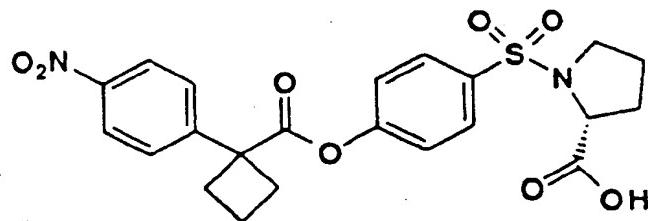
4-(2R-carboxypyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester



10 NMR (DMSO-d₆): δ 13.5-11.6 (1H, brs), 8.27 (2H, d, J=8.8Hz), 7.88 (2H, d, J=8.8Hz), 7.73 (2H, d, J=8.8Hz), 7.32 (2H, d, J=8.8Hz), 4.16 (1H, t, J=7.2Hz), 4.16-4.06 (1H, m), 3.5-3.0 (2H, m), 2.35-1.45 (6H, m), 0.92 (3H, t, J=7.2Hz);
TLC : Rf 0.43 (acetic acid:methanol:chloroform=1:2:40).

15 Example 2(29)

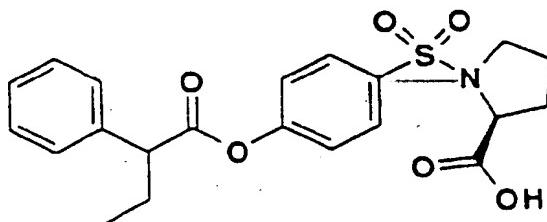
4-(2R-carboxypyrrolidin-1-ylsulfonyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester



25 NMR (DMSO-d₆): δ 12.9-12.6 (1H, brs), 8.28 (2H, d, J=8.8Hz), 7.87 (2H, d, J=8.8Hz), 7.71 (2H, d, J=8.8Hz),
7.31 (2H, d, J=8.8Hz), 4.16-4.04 (1H, m), 3.43-3.10 (2H, m), 3.10-2.90 (2H, m), 2.75-2.55 (2H, q-like), 2.28-1.46 (6H, m);
TLC : Rf 0.46 (acetic acid:methanol:chloroform=1:2:40).

30 Example 2(30)

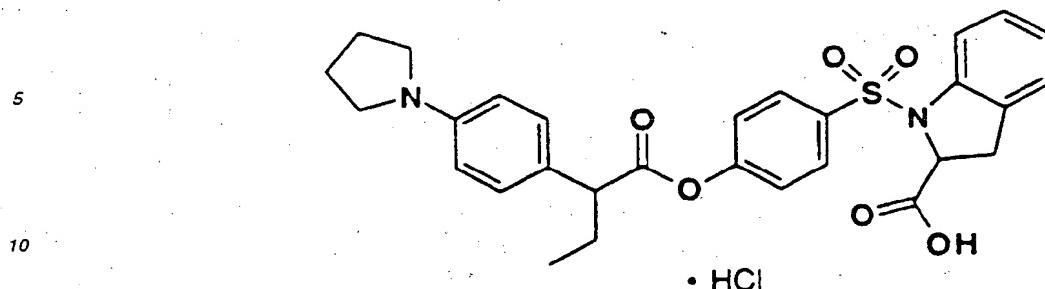
35 4-(2S-carboxypyrrolidin-1-ylsulfonyl)phenyl 2RS-phenylbutanoic acid ester



45 NMR (CDCl₃): δ 7.93-7.83 (2H, m), 7.50-7.14 (5H, m), 7.23-7.14 (2H, m), 7.14-6.70 (1H, brs), 4.26 (1H, dd,
J=10Hz, 5Hz), 3.71 (1H, t, J=7Hz), 3.56-3.43 (1H, m), 3.33-3.17 (1H, m), 2.35-1.65 (6H, m), 0.98 (3H, t, J=7Hz);
TLC : Rf 0.67 (acetic acid-methanol:chloroform=1:3:30).

50 Example 2(31)

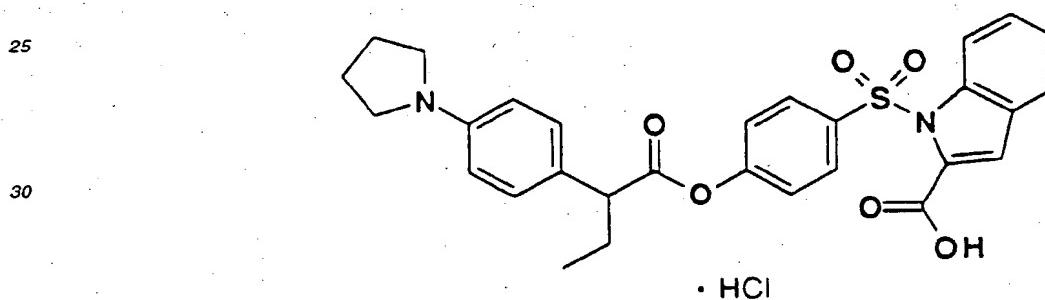
4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



15 NMR (CDCl_3): δ 7.73 (2H, d, $J=8.6\text{Hz}$), 7.58 (1H, d, $J=8.2\text{Hz}$), 7.17 (2H, d, $J=8.6\text{Hz}$), 7.12-6.94 (5H, m), 6.53 (2H, d, $J=8.8\text{Hz}$), 4.73 (1H, dd, $J=8.9\text{Hz}$ and 6.8Hz), 3.54 (1H, t, $J=7.8\text{Hz}$), 3.35-3.21 (4H, m), 3.17 (2H, d, $J=6.8\text{Hz}$), 2.25-1.70 (2H, m), 2.05-1.94 (4H, m), 0.95 (3H, t, $J=7.2\text{Hz}$);
TLC : Rf 0.46 (acetic acid:methanol:chloroform=1:2:40).

20 Example 2(32)

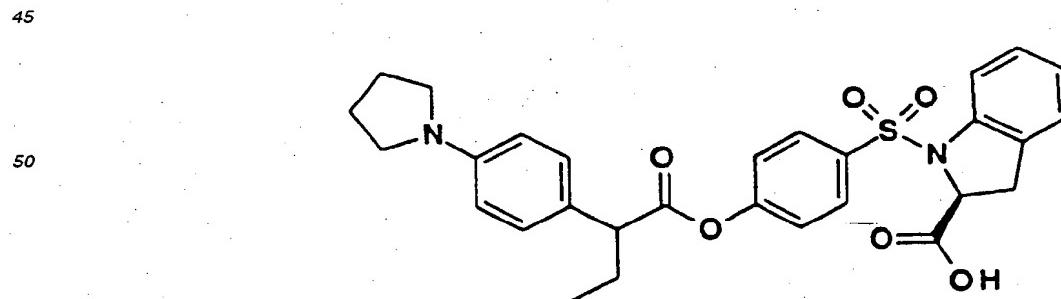
4-(2-carboxyindol-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



35 NMR (DMSO-d_6): δ 8.08 (2H, d, $J=8.8\text{Hz}$), 8.01 (1H, d, $J=8.4\text{Hz}$), 7.68 (1H, d, $J=8.0\text{Hz}$), 7.46 (1H, m), 7.40-7.16 (2H, m), 7.24 (2H, d, $J=8.8\text{Hz}$), 7.20 (2H, d, $J=8.6\text{Hz}$), 6.85-6.60 (2H, m), 3.69 (1H, t, $J=7.4\text{Hz}$), 3.40-3.15 (4H, m), 2.20-1.84 (5H, m), 1.84-1.60 (1H, m), 0.86 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.20 (chloroform:methanol:water=9:1:0.1).

40 Example 2(33)

4-(2S-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



NMR (CDCl_3): δ 7.72 (2H, d, $J=8.6\text{Hz}$), 7.57 (1H, d, $J=7.8\text{Hz}$), 7.17 (2H, d, $J=8.6\text{Hz}$), 7.28-6.88 (5H, m), 6.53 (2H, d, $J=8.6\text{Hz}$), 4.72 (1H, dd, $J=5.8\text{Hz}$ and 9.1Hz), 3.54 (1H, t, $J=7.8\text{Hz}$), 3.35-3.22 (4H, m), 3.22-3.08 (2H, m),

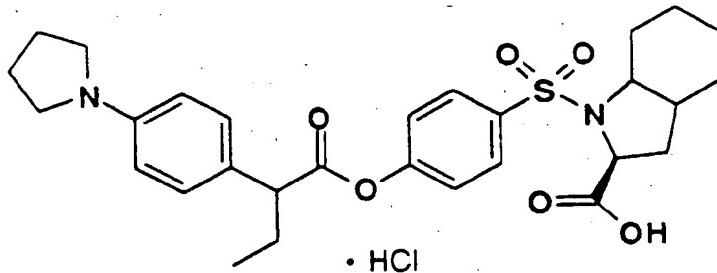
2.25-1.70 (2H, m), 2.05-1.95 (4H, m), 0.95 (3H, t, J=7.2Hz);
 TLC : Rf 0.46 (acetic acid:methanol:chloroform=1:2:40).

Example 2(34)

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4-(2S-carboxyperhydroindol-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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15

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NMR (CDCl_3): δ 7.89 (2H, d, J=8.8Hz), 7.71 (2H, d, J=8.6Hz), 7.51 (2H, d, J=8.6Hz), 7.17 (2H, d, J=8.8Hz), 4.20 (1H, t, J=8.6Hz), 4.0-3.5 (6H, m), 2.5-2.2 (4H, m), 2.4-1.0 (13H, m), 0.99 (3H, t, J=7.4Hz);
 TLC : Rf 0.60 (chloroform:methanol:acetic acid=40:2:1).

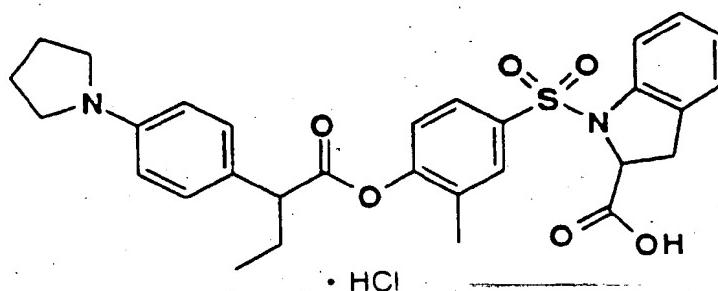
25

Example 2(35)

30

4-(2RS-carboxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

35



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45

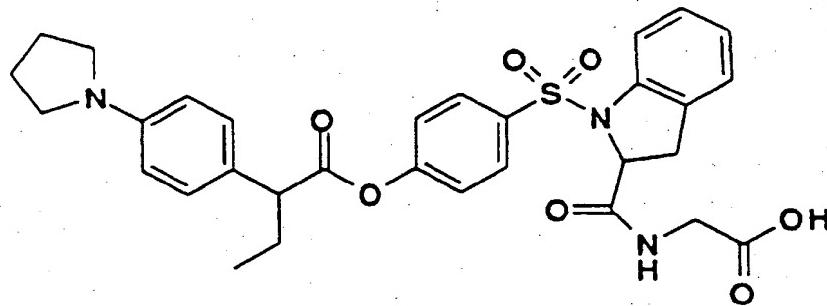
NMR (DMSO-d_6): δ 7.79 (1H, d-like), 7.67 (1H, dd, J=2.2 and 8.4Hz), 7.35-6.95 (7H, m), 6.71-6.67 (2H, m), 4.97 (1H, dd, J=4.4 and 10.7Hz), 3.71 (1H, t, J=7.6Hz), 3.35-2.96 (6H, m), 2.14-1.68 (2H, m), 2.00-1.94 (4H, m), 1.91 (3H, s), 0.87 (3H, t, J=7.2Hz);
 TLC : Rf 0.45 (chloroform:methanol:water=8:2:0.2).

50

Example 2(36)

4-(2RS-(N-carboxymethylcarbamoyl)indolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

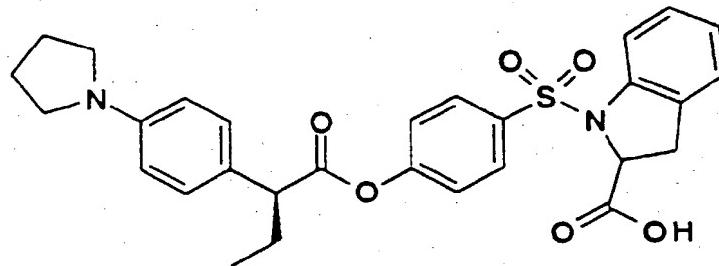
55



15 NMR (CDCl_3): δ 7.70 (1H, d, $J=7.8\text{Hz}$), 7.58 (2H, d, $J=8.8\text{Hz}$), 7.28-7.02 (8H, m), 6.66 (2H, d, $J=8.8\text{Hz}$), 4.64 (1H, dd, $J=10.4, 2.8\text{Hz}$), 4.02 (2H, d, $J=3.0\text{Hz}$), 3.56 (1H, t, $J=7.6\text{Hz}$), 3.37-3.05 (5H, m), 2.81 (1H, dd, $J=16.0, 10.4\text{Hz}$), 2.35-1.74 (6H, m), 0.95 (3H, t, $J=7.6\text{Hz}$);
TLC : Rf 0.33 (chloroform:methanol:acetic acid=40:2:1).

Example 2(37)

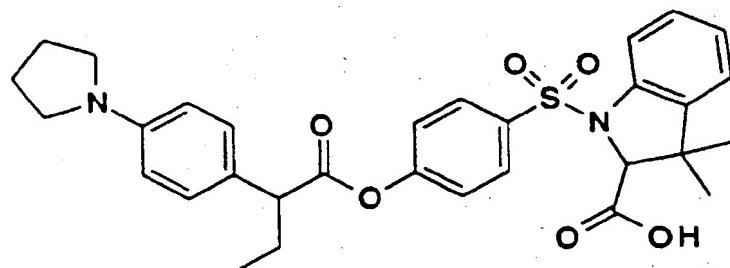
20 4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



35 NMR (CDCl_3): δ 7.72 (2H, d, $J=8\text{Hz}$), 7.59 (1H, d, $J=8\text{Hz}$), 7.27-7.03 (7H, m), 6.54 (2H, d, $J=8\text{Hz}$), 6.08 (1H, br), 4.77-4.69 (1H, m), 3.55 (1H, t, $J=8\text{Hz}$), 3.31-3.24 (4H, m), 3.19-3.15 (2H, m), 2.20-1.76 (2H, m), 2.03-1.96 (4H, m), 0.95 (3H, t, $J=8\text{Hz}$);
TLC : Rf 0.45 (chloroform:methanol:water=8:2:0.2).

40 Example 2(38)

4-(2RS-carboxy-3,3-dimethylindolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

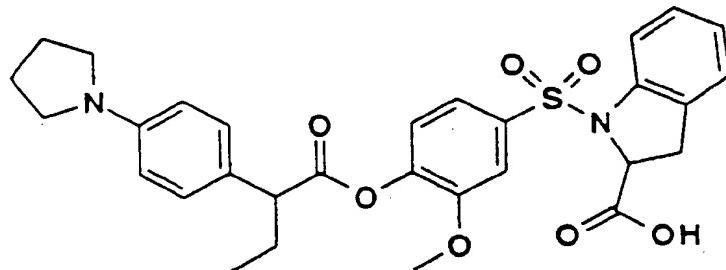


55 NMR (CDCl_3): δ 7.83 (2H, d, $J=8.5\text{Hz}$), 7.55 (1H, d, $J=8.0\text{Hz}$), 7.25-6.93 (3H, m), 7.17 (2H, d, $J=8.5\text{Hz}$), 7.09 (2H, d, $J=8.5\text{Hz}$), 6.53 (2H, d, $J=8.5\text{Hz}$), 4.36 (1H, s), 3.54 (1H, t, $J=8.0\text{Hz}$), 3.35-3.10 (4H, m), 2.05-1.90 (4H, m), 2.25-1.70 (2H, m), 1.31 (3H, s), 1.04 (3H, s), 0.94 (3H, t, $J=7.5\text{Hz}$);

TLC : Rf 0.48 (chloroform:methanol:acetic acid=40:2:1).

Example 2(39)

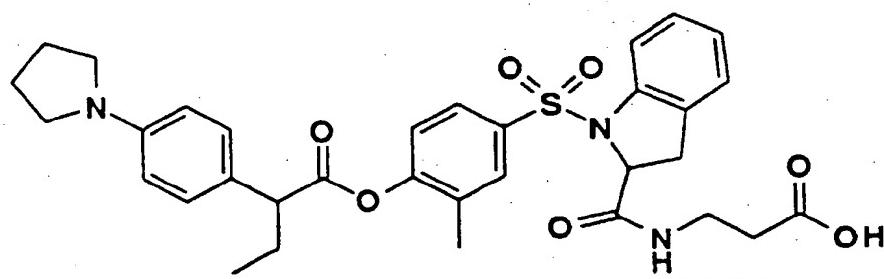
5 4-(2RS-carboxyindolin-1-ylsulfonyl)-2-methoxyphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



10 NMR (CDCl_3): δ 7.7-7.6 (m, 1H), 7.5-6.9 (m, 8H), 6.5-6.4 (m, 2H), 4.8-4.6 (m, 1H), 3.8-3.5 (m, 4H), 3.4-3.0 (m, 6H), 2.2-1.7 (m, 6H), 1.1-0.9 (m, 3H);
15 TLC : Rf 0.65 (chloroform:methanol=3:1).

20 Example 2(40)

25 4-(2RS-(N-2-carboxyethylcarbamoyl)indolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



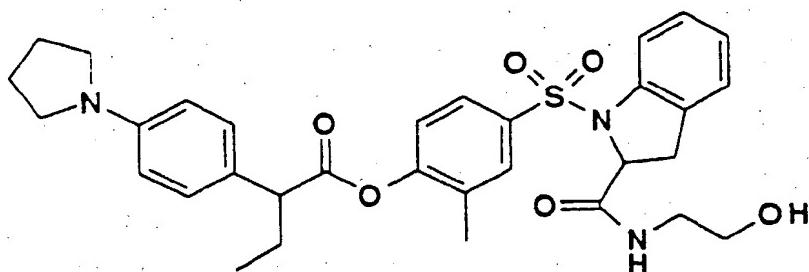
30 NMR (CDCl_3): δ 7.8-6.8 (m, 11H), 4.7-4.5 (m, 1H), 3.8-3.5 (m, 7H), 3.3-3.1 (m, 1H), 3.0-2.8 (m, 1H), 2.7-2.5 (m, 2H), 2.3-2.1 (m, 4H), 2.1-1.8 (m, 5H), 0.97 (t, J=7.2Hz, 3H);
35 TLC : Rf 0.76 (methanol:chloroform=1:3).

40 Example 2(41)

45 4-(2RS-(N-2-hydroxyethylcarbamoyl)indolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

50

55

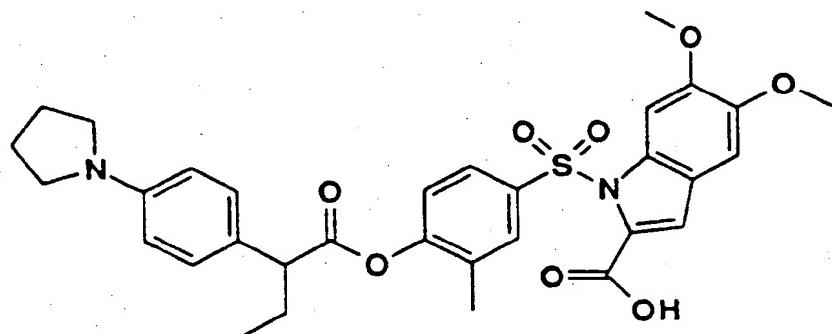


15 NMR (CDCl_3): δ 7.72 (1H, d, $J=8.0\text{Hz}$), 7.45-6.92 (9H, m), 6.51 (2H, d, $J=8.6\text{Hz}$), 4.57 (1H, dd, $J=2.8, 10.6\text{Hz}$),
3.77-3.52 (5H, m), 3.39-3.17 (5H, m), 2.88 (1H, dd, $J=10.6, 16.8\text{Hz}$), 2.23-1.78 (6H, m), 1.92 (3H, s), 0.96 (3H, t,
 $J=7.4\text{Hz}$);

TLC : Rf 0.43 (chloroform:methanol:acetic acid=25:5:1).

Example 2(42)

20 4-(2-carboxy-5,6-dimethoxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

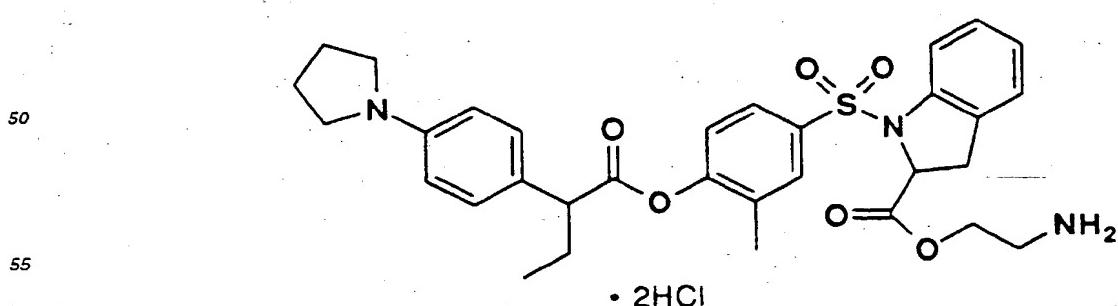


35 NMR (CDCl_3): δ 7.78-7.62 (3H, m), 7.35 (1H, s), 7.18 (2H, d, $J=9\text{Hz}$), 7.00 (1H, d, $J=8\text{Hz}$), 6.95 (1H, s), 6.52 (2H,
d, $J=9\text{Hz}$), 4.00 (3H, s), 3.91 (3H, s), 3.70-3.10 (1H, brs), 3.57 (1H, t, $J=7\text{Hz}$), 3.35-3.18 (4H, m), 2.25-1.75 (9H, m),
0.96 (3H, t, $J=7\text{Hz}$).

TLC : Rf 0.19 (ethyl acetate:hexane:acetic acid=5:10:0.5).

40 Example 2(43)

45 4-(2RS-(2-aminoethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic
acid ester · 2hydrochloride



EP 0 769 498 A1

NMR (DMSO-d₆): 8.83 (2H, brs), 7.76 (1H, s), 7.66 (1H, d, J=8.0Hz), 7.37 (1H, d, J=8.0Hz), 7.23-7.00 (6H, m), 6.70 (2H, d, J=8.0Hz), 5.08 (1H, dd, J=6.2, 9.4Hz), 4.37-4.32 (2H, m), 3.69 (1H, t, J=7.2Hz), 3.35-3.07 (8H, m), 2.14-1.69 (9H, m), 0.89 (3H, t, J=7.2Hz);

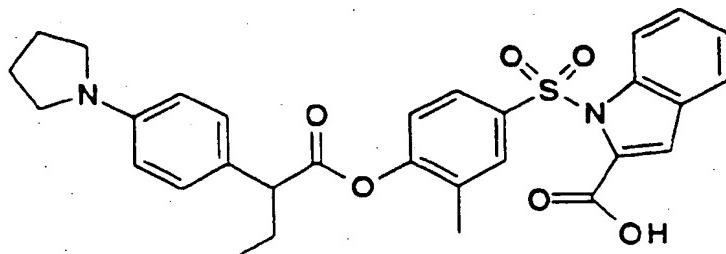
TLC : Rf 0.46 (chloroform:methanol:acetic acid=25:5:1).

5

Example 2(44)

4-(2-carboxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

10



20

NMR (CDCl_3): δ 8.13 (1H, d, $J=9\text{Hz}$), 7.90-7.78 (2H, m), 7.60 (1H, d, $J=9\text{Hz}$), 7.46 (1H, td, $J=8.1\text{Hz}$), 7.39 (1H, s), 7.35-7.25 (1H, m), 7.21 (2H, d, $J=9\text{Hz}$), 6.75-6.50 (2H, m), 3.59 (1H, t, $J=7\text{Hz}$), 3.38-3.23 (4H, m), 3.23-2.90 (1H, brs), 2.25-1.75 (6H, m), 0.96 (3H, t, $J=7\text{Hz}$);

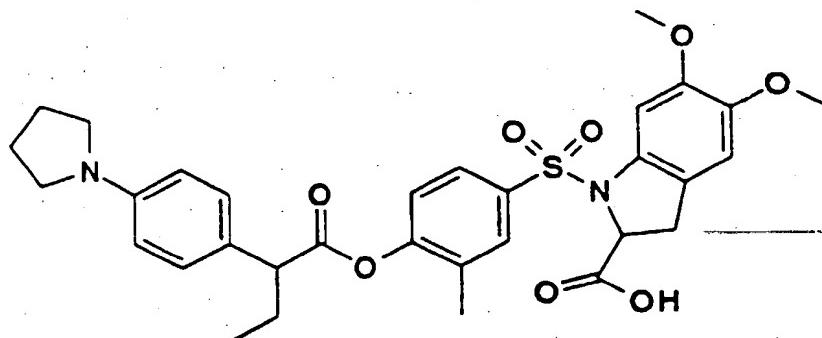
TLC : Rf 0.20 (ethyl acetate:hexane:acetic acid=5:10:0.5).

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Example 2(45)

4-(2RS-carboxy-5,6-dimethoxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR ($\text{CDCl}_3 + \text{CD}_3\text{OD}$): δ 7.6-7.4 (m, 2H), 7.26 (s, 1H), 7.19 (d, $J=8.7\text{Hz}$, 2H), 6.96 (dd, $J=1.2, 8.4\text{Hz}$, 1H), 6.58 (s, 1H), 6.54 (d, $J=8.7\text{Hz}$, 2H), 4.7-4.6 (m, 1H), 3.91 (s, 3H), 3.79 (s, 3H), 3.58 (t, $J=7.7\text{Hz}$, 1H), 3.4-3.2 (m, 4H), 3.1-2.9 (m, 2H), 2.3-1.8 (m, 6H), 1.94 (s, 3H), 0.96 (t, $J=7.4\text{Hz}$, 3H);

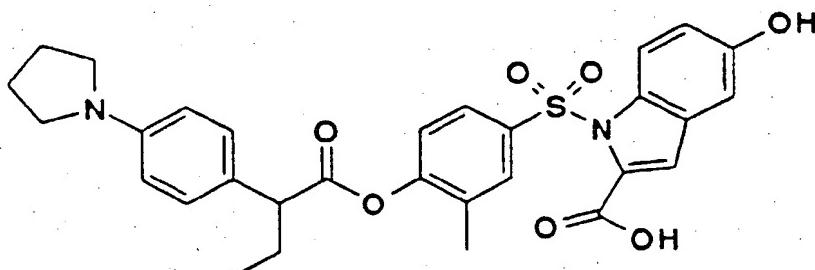
TLC : Rf 0.45 (chloroform:methanol=4:1).

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Example 2(46)

4-(2-carboxy-5-hydroxvindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

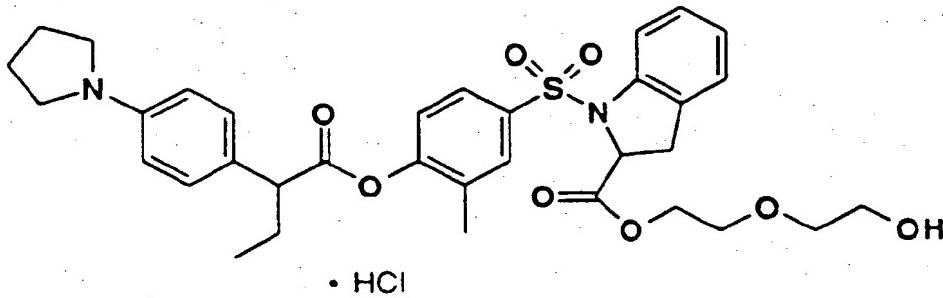
55



NMR (CD_3OD): δ 7.85-7.63 (3H, m), 7.03 (2H, d, $J=8\text{Hz}$), 6.93 (1H, d, $J=8\text{Hz}$); 6.87-6.70 (3H, m), 6.53 (2H, d, $J=8\text{Hz}$), 3.56 (1H, t, $J=7\text{Hz}$), 3.30-3.10 (4H, m), 2.20-1.90 (5H, m), 1.90-1.65 (1H, m), 1.84 (3H, s), 0.91 (3H, t, $J=7\text{Hz}$);
15 TLC : Rf 0.23 (ethyl acetate:hexane:acetic acid=10:10:0.5).

Example 2(47)

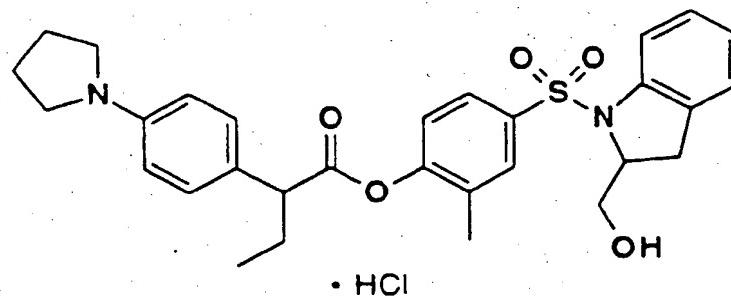
20 4-(2RS-(2-(2-hydroxyethoxy)ethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



35 NMR (CDCl_3): δ 7.61-7.51 (3H, m), 7.23-7.10 (3H, m), 7.10-6.95 (3H, m), 6.51 (2H, d, $J=8.0\text{Hz}$), 4.75 (1H, dd, $J=5.6, 10.2\text{Hz}$), 4.38-4.33 (2H, m), 3.75-3.51 (7H, m), 3.30-3.22 (5H, m), 3.09 (1H, dd, $J=5.6, 16.6\text{Hz}$), 2.23-1.78 (6H, m), 1.96 (3H, s), 0.96 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.65 (chloroform:methanol=15:1).

40 Example 2(48)

45 4-(2RS-hydroxymethylindolin-1-ylsulfonyl)-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



NMR (DMSO-d_6): δ 7.60 (1H, s-like), 7.51-7.40 (2H, m), 7.22-6.97 (6H, m), 6.51 (2H, d, $J=8\text{Hz}$), 4.40-4.24 (1H,

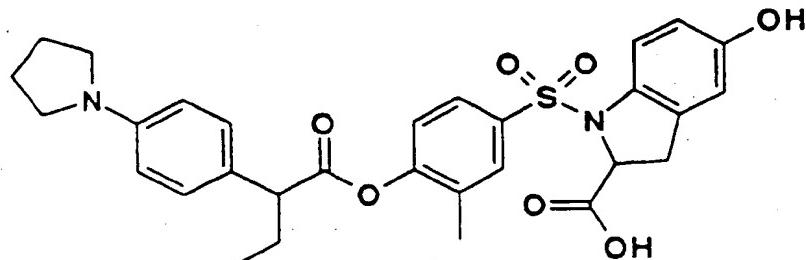
EP 0 769 498 A1

m), 3.68-3.37 (3H, m), 3.65 (1H, t, J=7Hz), 3.23-3.17 (4H, m), 2.87-2.69 (2H, m), 2.19-1.62 (each 1H, m), 1.99-1.93 (4H, m), 1.86 (3H, s), 0.87 (3H, t, J=7Hz);

TLC : Rf 0.29 (hexane:ethyl acetate=2:1).

5 Example 2(49)

4-(2RS-carboxy-5-hydroxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

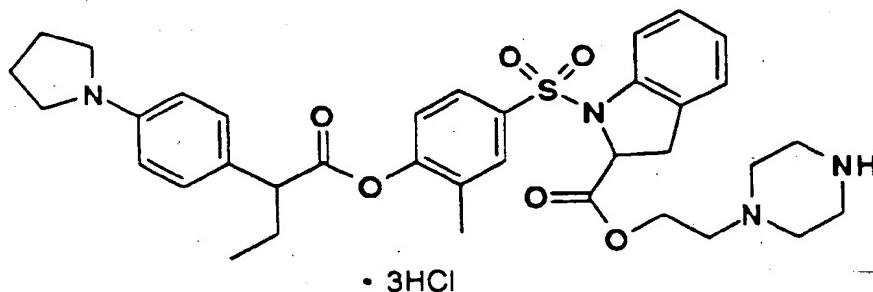


20 NMR (CDCl_3 +3 drops of CD_3OD): δ 7.5-7.4 (m, 3H), 7.2-7.1 (m, 3H), 7.0-6.9 (m, 1H), 6.5-6.4 (m, 3H), 4.7-4.6 (m, 1H), 3.58 (t, J=7.8Hz, 1H), 3.4-3.2 (m, 4H), 3.1-2.9 (m, 2H), 2.2-1.8 (m, 6H), 1.94 (s, 3H), 0.97 (t, J=7.2Hz, 3H);
TLC : Rf 0.2 (chloroform:methanol=6:1).

Example 2(50)

25 4-(2RS-(2-(piperazin-1-yl)ethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 3hydrochloride

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45 NMR (CD_3OD): δ 7.72-7.64 (3H, m), 7.57-7.49 (4H, m), 7.26-7.00 (4H, m), 5.12 (1H, dd, J=6.0, 8.8Hz), 4.63-4.59 (2H, m), 3.90 (1H, t, J=8.0Hz), 3.77-3.59 (14H, m), 3.23-3.20 (2H, m), 2.32-1.83 (6H, m), 1.96 (3H, s), 0.97 (3H, t, J=7.4Hz);

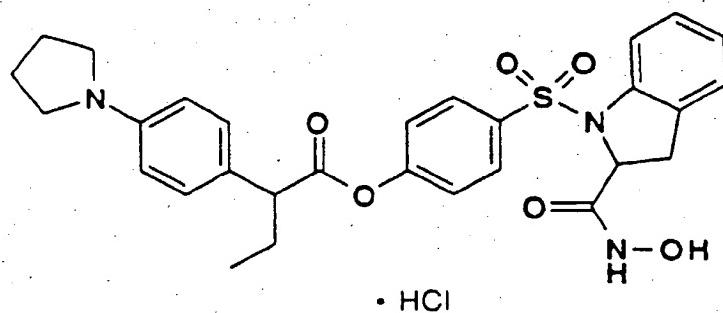
TLC : Rf 0.41 (chloroform:methanol:acetic acid=25:5:1).

Example 2(51)

50 4-(2RS-(N-hydroxycarbamoyl)indolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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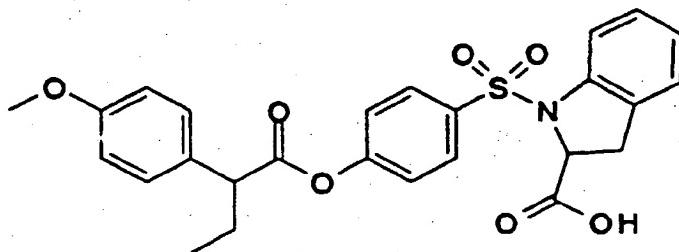
NMR (CD_3OD): δ 7.75 (2H, d, $J=8.6\text{Hz}$), 7.60 (1H, d, $J=8.0\text{Hz}$), 7.58-7.48 (4H, m), 7.21 (1H, dd, $J=6.5\text{Hz}, 1.5\text{Hz}$), 7.12 (2H, d, $J=8.6\text{Hz}$), 7.09-7.01 (2H, m), 4.68 (1H, dd, $J=9.0\text{Hz}, 5.0\text{Hz}$), 3.87 (1H, t, $J=7.0\text{Hz}$), 3.77-3.70 (4H, m), 3.03-2.98 (2H, m), 2.28-2.23 (4H, m), 2.20-2.13 (0.5H, m), 1.97-1.81 (1.5H, m), 0.90 (3H, t, $J=7.0\text{Hz}$);
TLC : R_f 0.49 (hexane:ethyl acetate:acetic acid=8:8:1).

20 Example 2(52)

4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(4-methoxyphenyl)butanoic acid ester

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NMR (CDCl_3): δ 7.74 (2H, d, $J=8.8\text{Hz}$), 7.58 (1H, d, $J=8.0\text{Hz}$), 7.29-7.02 (7H, m), 6.87 (2H, d, $J=8.8\text{Hz}$), 4.90 (1H, brs), 4.73 (1H, dd, $J=9.2, 5.8\text{Hz}$), 3.80 (3H, s), 3.60 (1H, t, $J=7.8\text{Hz}$), 3.20-3.15 (2H, m), 2.23-2.05 (1H, m), 1.94-1.76 (1H, m), 0.951 (3H, t, $J=7.6\text{Hz}$);
TLC : R_f 0.36 (chloroform:methanol:acetic acid=40:2:1).

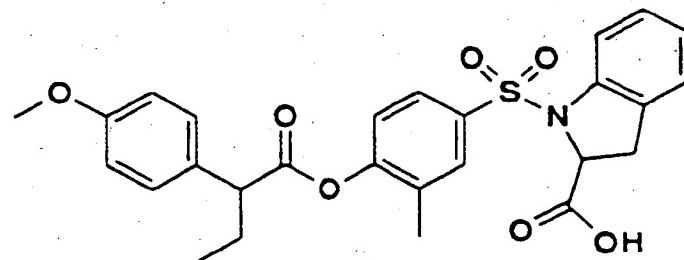
40 Example 2(53)

4-(2RS-carboxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester

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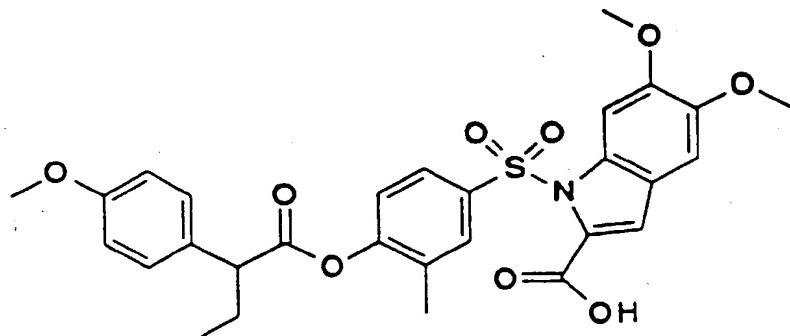


NMR (DMSO-d_6): δ 7.82 (1H, d-like), 7.72 (1H, d-like), 7.38 (2H, d, $J=8.6\text{Hz}$), 7.32 (1H, d, $J=7.8\text{Hz}$), 7.23-7.10 (3H, m), 7.03-6.96 (3H, m), 4.73 (1H, dd, $J=5.2$ and 9.3Hz), 3.88 (1H, t, $J=7.6\text{Hz}$), 3.82 (3H, s), 3.14-3.05 (2H, m), 2.25-2.10 and 1.96-1.79 (each 1H, m), 0.96 (3H, t, $J=7.2\text{Hz}$);

TLC : Rf 0.41 (chloroform:methanol:water=8:2:0.2).

Example 2(54)

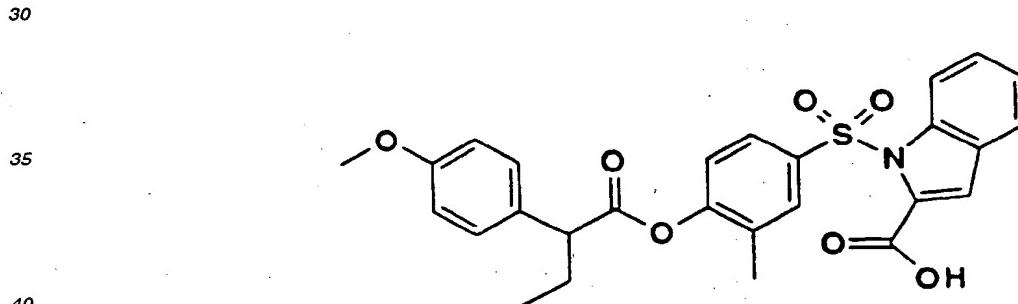
5 4-(2-carboxy-5,6-dimethoxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester



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20 NMR (CDCl_3): δ 7.79-7.64 (3H, m), 7.36 (1H, s), 7.23 (2H, d, $J=9\text{Hz}$), 7.01 (1H, d, $J=9\text{Hz}$), 6.96 (1H, s), 6.88 (2H, d, $J=9\text{Hz}$), 4.00 (3H, s), 3.91 (3H, s), 3.80 (3H, s), 3.64 (1H, t, $J=7\text{Hz}$), 2.27-2.03 (1H, m), 2.00-1.80 (1H, m), 1.96 (3H, s), 0.96 (3H, t, $J=7\text{Hz}$);
25 TLC : Rf 0.10 (ethyl acetate:hexane:acetic acid=5:10:0.5).

Example 2(55)

4-(2-carboxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester

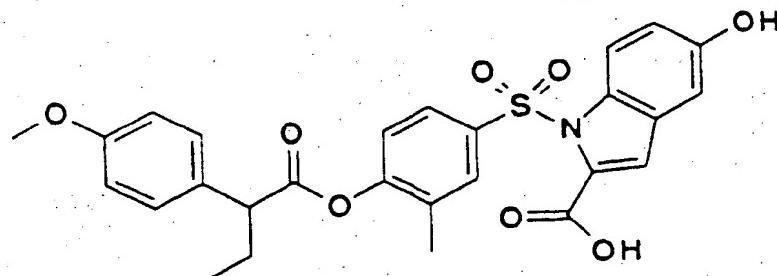


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40 NMR (CDCl_3): δ 8.14 (1H, d, $J=9\text{Hz}$), 7.90-7.78 (2H, m), 7.60 (1H, d, $J=9\text{Hz}$), 7.52-7.40 (1H, m), 7.38 (1H, s), 7.35-7.20 (3H, m), 7.03 (1H, d, $J=9\text{Hz}$), 6.87 (2H, d, $J=9\text{Hz}$), 3.79 (3H, s), 3.64 (1H, t, $J=7\text{Hz}$), 2.28-2.05 (1H, m), 2.00-1.79 (1H, m), 1.96 (3H, s), 0.96 (3H, t, $J=7\text{Hz}$);
45 TLC : Rf 0.26 (ethyl acetate:hexane:acetic acid=5:10:0.5).

Example 2(56)

50 4-(2-carboxy-5-hydroxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester

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NMR (CDCl_3): δ 7.94 (1H, d, $J=9\text{Hz}$), 7.80-7.69 (2H, m), 7.26 (2H, d, $J=9\text{Hz}$), 7.17 (1H, s), 6.99 (1H, d, $J=9\text{Hz}$),
6.96 (1H, dd, $J=9,2\text{Hz}$), 6.87 (2H, d, $J=9\text{Hz}$), 6.87 (1H, d, $J=2\text{Hz}$), 3.80-3.40 (1H, brs), 3.79 (3H, s), 3.64 (1H, t, $J=7\text{Hz}$),
2.26-2.05 (1H, m), 2.00-1.75 (1H, m), 1.93 (3H, s), 0.95 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.16 (ethyl acetate:hexane:acetic acid=10:10:0.5).

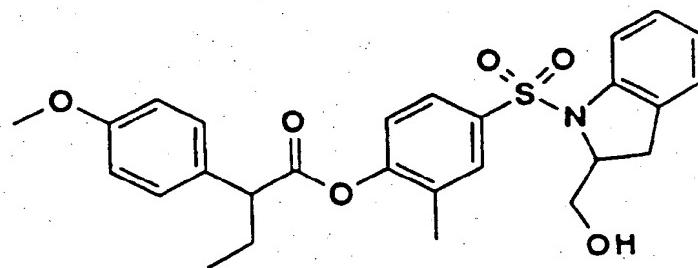
Example 2(57)

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4-(2RS-hydroxymethylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester

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NMR (DMSO-d_6): δ 7.61 (1H, s-like), 7.50-7.40 (2H, m), 7.28 (2H, d, $J=8\text{Hz}$), 7.21-6.96 (4H, m), 6.92 (2H, d,
 $J=8\text{Hz}$), 5.02 (1H, t-like), 4.32 (1H, m), 3.78 (1H, t, $J=7\text{Hz}$), 3.74 (3H, s), 3.67-3.57 and 3.47-3.37 (each 1H, m), 2.83-2.70
(2H, m), 2.10-1.95 and 1.86-1.65 (each 1H, m), 1.85 (3H, s), 0.88 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.21 (hexane:ethyl acetate=2:1).

Example 2(58)

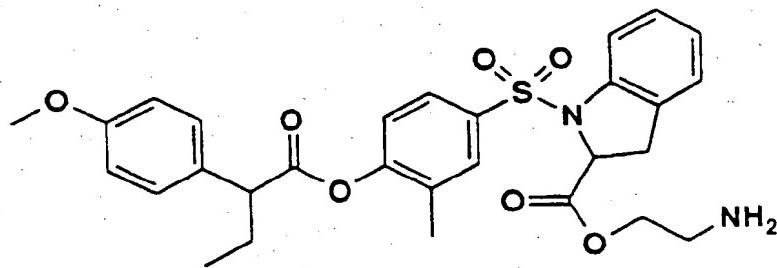
40

4-(2RS-(2-aminoethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid es-
ter · hydrochloride

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· HCl

NMR (DMSO-d_6): δ 8.25 (3H, brs), 7.78-7.65 (2H, m), 7.39-7.00 (5H, m), 7.28 (2H, d, $J=8.8\text{Hz}$), 6.91 (2H, d,

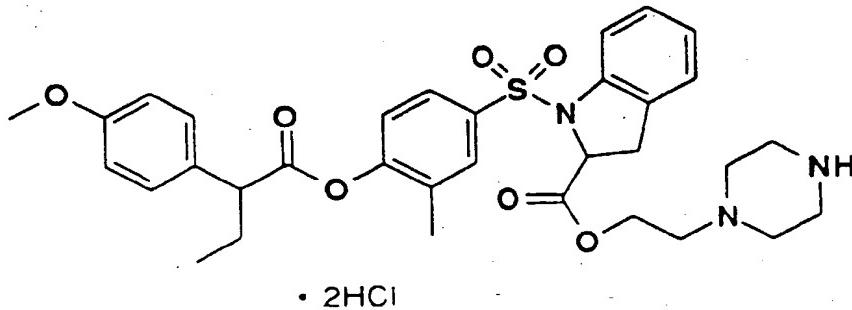
EP 0 769 498 A1

J=8.8Hz), 5.08 (1H, dd, J=5.8, 10.0Hz), 4.34 (2H, t, J=5.2Hz), 3.83-3.74 (1H, m), 3.74 (3H, s), 3.30-3.09 (4H, m), 2.17-1.75 (2H, m), 1.90 (3H, s), 0.89 (3H, t, J=7.2Hz);
 TLC : Rf 0.53 (chloroform:methanol:acetic acid=25:5:1).

5 Example 2(59)

4-(2RS-(2-(piperazin-4-yl)ethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester · 2hydrochloride

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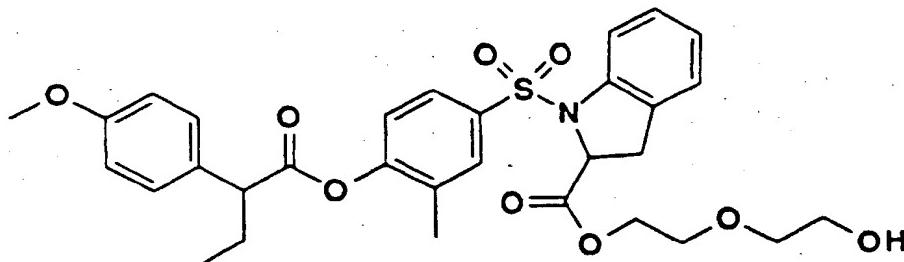


NMR (CD_3OD) : δ 7.68-7.63 (2H, m), 7.51 (1H, d, J=7.8Hz), 7.27 (2H, d, J=8.4Hz), 7.22-7.02 (4H, m), 6.90 (2H, d, J=8.4Hz), 5.10 (1H, t, J=7.2Hz), 4.60 (2H, brs), 3.78 (3H, s), 3.75-3.19 (13H, m), 2.23-1.78 (2H, m), 1.89 (3H, s), 0.95 (3H, t, J=7.4Hz);
 TLC : Rf 0.16 (chloroform:methanol=10:1).

Example 2(60)

30 4-(2RS-(2-(2-hydroxyethoxy)ethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester

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40

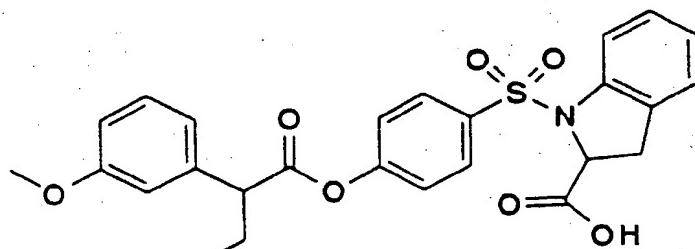


45 NMR (CDCl_3): δ 7.62-7.51 (3H, m), 7.26 (2H, d, J=8.4Hz), 7.28-6.96 (4H, m), 6.87 (2H, d, J=8.4Hz), 4.76 (1H, dd, J=5.4, 10.6Hz), 4.38-4.34 (2H, m), 3.80 (3H, s), 3.75-3.55 (7H, m), 3.31-3.04 (2H, m), 2.26-1.80 (2H, m), 1.93 (3H, s), 0.97 (3H, t, J=7.4Hz);
 TLC : Rf 0.11(hexane:ethyl acetate=1:1).

50 Example 2(61)

4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(3-methoxyphenyl)butanoic acid ester

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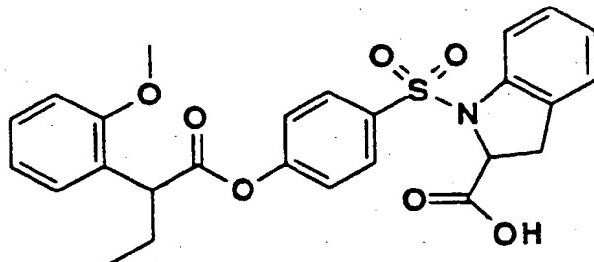
NMR (CDCl_3): δ 7.75 (2H, d, $J=8.8\text{Hz}$), 7.57 (1H, d, $J=7.8\text{Hz}$), 7.30-6.79 (9H, m), 4.73 (1H, t, $J=8.0\text{Hz}$), 3.80 (3H, s), 3.62 (1H, t, $J=7.8\text{Hz}$), 3.20-3.17 (2H, m), 2.28-2.05 (1H, m), 1.99-1.77 (1H, m), 0.96 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.66 (chloroform:methanol:acetic acid=40:2:1).

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Example 2(62)

4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(2-methoxyphenyl)butanoic acid ester

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NMR (CDCl_3): δ 7.75 (2H, d, $J=8.8\text{Hz}$), 7.58 (1H, d, $J=8.0\text{Hz}$), 7.25 (2H, d, $J=8.8\text{Hz}$), 7.31-6.87 (7H, m), 4.74 (1H, t, $J=8.0\text{Hz}$), 4.04 (1H, t, $J=7.2\text{Hz}$), 3.84 (3H, s), 3.18 (2H, brd, $J=7.2\text{Hz}$), 2.22-2.05 (1H, m), 1.96-1.74 (1H, m), 0.95 (3H, t, $J=7.6\text{Hz}$);

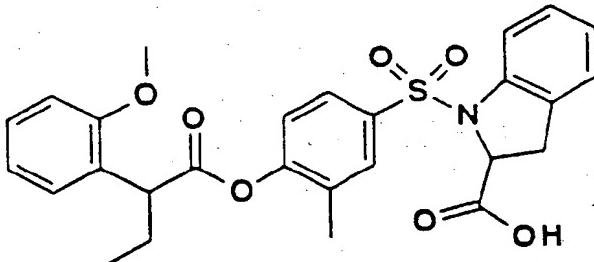
35

TLC : Rf 0.48 (chloroform:methanol:acetic acid=40:2:1).

Example 2(63)

4-(2RS-carboxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(2-methoxyphenyl)butanoic acid ester

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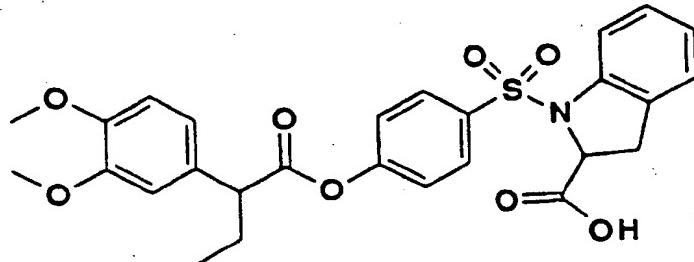


NMR (DMSO-d_6): δ 13.19 (1H, br), 7.79 (1H, d, $J=2.0\text{Hz}$), 7.68 (1H, dd, $J=2.0$ and 8.5Hz), 7.36-6.92 (9H, m), 4.96 (1H, dd, $J=4.2$ and 10.9Hz), 4.08 (1H, t, $J=7.6\text{Hz}$), 3.80 (3H, s), 3.39-2.96 (2H, m), 2.19-1.69 (2H, m), 1.95 (3H, s), 0.87 (3H, t, $J=7.2\text{Hz}$);

TLC : Rf 0.39 (chloroform:methanol:water=8:2:0.2).

Example 2(64)

4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(3,4-dimethoxyphenyl)butanoic acid ester

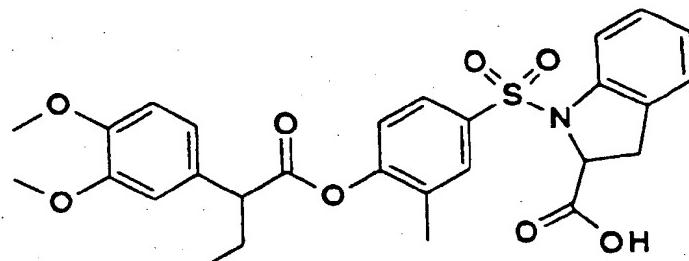


NMR (CDCl_3): δ 7.76 (2H, d, $J=8.8\text{Hz}$), 7.57 (1H, d, $J=8.0\text{Hz}$), 7.25-7.02 (5H, m), 6.86-6.85 (3H, m), 4.73 (1H, t, $J=8.0\text{Hz}$), 3.87 (6H, s), 3.59 (1H, t, $J=7.8\text{Hz}$), 3.21-3.17 (2H, brd), 2.24-2.05 (1H, m), 1.97-1.76 (1H, m), 0.97 (3H, t, $J=7.6\text{Hz}$);

TLC : Rf 0.50 (chloroform:methanol:acetic acid=40:2:1).

Example 2(65)

4-(2RS-carboxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(3,4-dimethoxyphenyl)butanoic acid ester

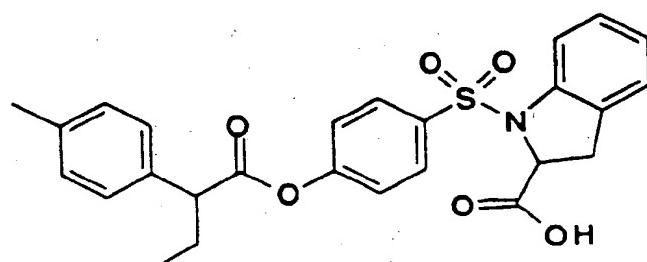


NMR (DMSO-d_6): δ 13.14 (1H, br), 7.80 (1H, s), 7.68 (1H, d-like), 7.35-7.11 (4H, m), 7.02-6.86 (4H, m), 4.97 (1H, dd, $J=4.2$ and 10.5Hz), 3.79 (1H, t, $J=7.4\text{Hz}$), 3.74 (6H, s), 3.39-2.97 (2H, m), 2.16-1.98 and 1.95-1.72 (each 1H, m), 1.91 (3H, s), 0.89 (3H, t, $J=7.2\text{Hz}$);

TLC : Rf 0.39 (chloroform:methanol:water=8:2:0.2).

Example 2(66)

4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(4-methylphenyl)butanoic acid ester



NMR (CDCl_3): δ 7.74 (2H, d, $J=8.8\text{Hz}$), 7.58 (1H, d, $J=8.0\text{Hz}$), 7.24-7.02 (9H, m), 4.74 (1H, t, $J=8.6\text{Hz}$), 3.62 (1H,

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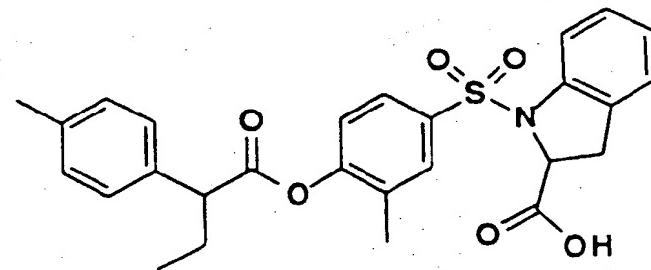
t, J=7.8Hz), 3.18 (2H, brd), 2.34 (3H, s), 2.27-2.05 (1H, m), 1.97-1.75 (1H, m), 0.96 (3H, t, J=7.4Hz);
 TLC : Rf 0.43 (chloroform:methanol:acetic acid=40:2:1).

Example 2(67)

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4-(2RS-carboxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester

10



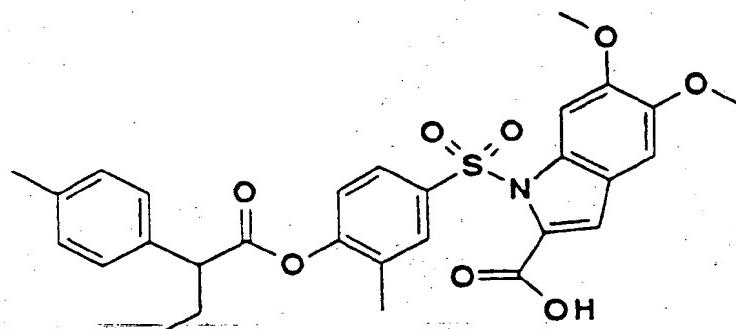
15

20 NMR (DMSO-d₆): δ 13.08 (1H, br), 7.73 (1H, d, J=2.0Hz), 7.61 (1H, dd, J=2.0 and 8.6Hz), 7.28-6.87 (9H, m),
 4.90 (1H, dd, J=4.0 and 10.8Hz), 3.75 (1H, t, J=7.6Hz), 3.32-2.90 (2H, m), 2.22 (3H, s), 2.13-1.91 and 1.86-1.64 (each
 1H, m), 1.82 (3H, s), 0.80 (3H, t, J=7.2Hz);
 TLC Rf 0.43 (chloroform:methanol:water=8:2:0.2).

25 Example 2(68)

4-(2-carboxy-5,6-dimethoxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester

30



35

40 NMR (CDCl₃): δ 7.78-7.64 (3H, m), 7.35 (1H, s), 7.23 (2H, d, J=9Hz), 7.15 (2H, d, J=9Hz), 7.00 (1H, d, J=9Hz),
 6.95 (1H, s), 4.00 (3H, s), 3.91 (3H, s), 3.85-3.30 (1H, br), 3.65 (1H, t, J=7Hz), 2.33 (3H, s), 2.30-2.10 (1H, m), 2.00-1.80
 (1H, m), 1.96 (3H, s), 0.96 (3H, t, J=7Hz);
 45 TLC : Rf 0.23 (ethyl acetate:hexane:acetic acid=5:10:0.5).

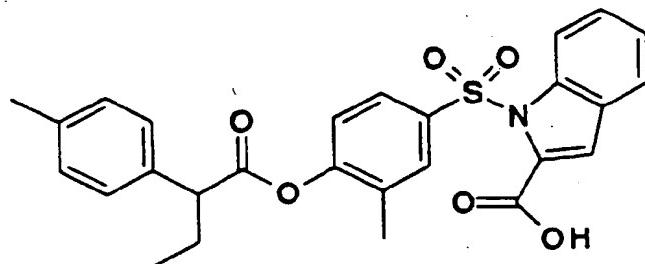
Example 2(69)

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4-(2-carboxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester

55

5



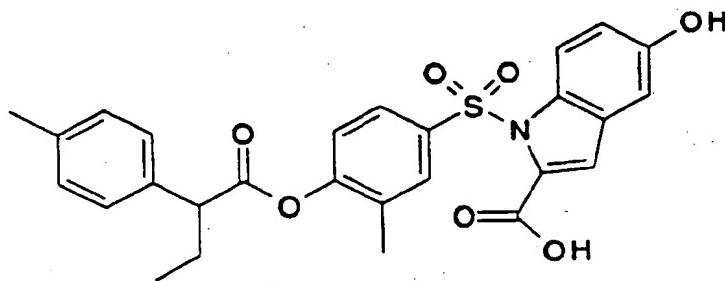
10

NMR (CDCl_3): δ 8.14 (1H, d, $J=9\text{Hz}$), 7.90-7.78 (2H, m), 7.60 (1H, d, $J=9\text{Hz}$), 7.52-7.41 (1H, m), 7.39 (1H, s),
7.35-7.10 (5H, m), 7.03 (1H, d, $J=9\text{Hz}$), 4.00-3.60 (1H, br), 3.66 (1H, t, $J=7\text{Hz}$), 2.33 (3H, s), 2.30-2.07 (1H, m), 2.00-1.75
15 (1H, m), 1.97 (3H, s), 0.96 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.28 (ethyl acetate:hexane:acetic acid=5:10:0.5).

Example 2(70)

20 4-(2-carboxy-5-hydroxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester

25



30

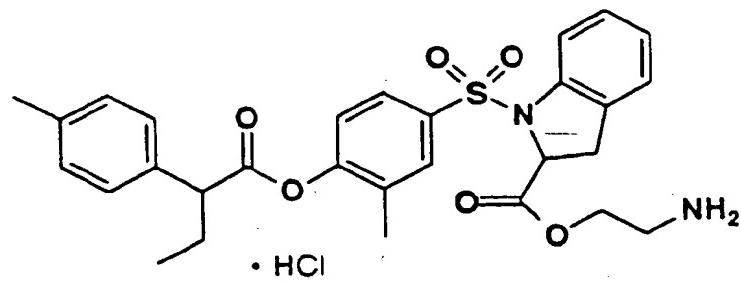
35 NMR (CDCl_3): δ 7.95 (1H, d, $J=9\text{Hz}$), 7.81-7.69 (2H, m), 7.22 (2H, d, $J=8\text{Hz}$), 7.20 (1H, s), 7.15 (2H, d, $J=8\text{Hz}$),
7.00 (1H, d, $J=8\text{Hz}$), 6.97 (1H, dd, $J=9,2\text{Hz}$), 6.89 (1H, d, $J=2\text{Hz}$), 3.80-3.30 (1H, br), 3.66 (1H, t, $J=7\text{Hz}$), 2.33 (3H,
s), 2.28-2.10 (1H, m), 2.00-1.80 (1H, m), 1.94 (3H, s), 0.96 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.24 (ethyl acetate:hexane:acetic acid=10:10:0.5).

Example 2(71)

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40 4-(2RS-(2-aminoethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester
hydrochloride

45



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55 NMR ($\text{CDCl}_3+\text{CD}_3\text{OD}$): δ 7.8-7.5 (m, 4H), 7.3-7.0 (m, 7H), 5.0-4.8 (m, 1H), 4.6-4.4 (m, 2H), 3.67 (t, $J=9.2\text{Hz}$,
1H), 3.4-3.3 (m, 2H), 3.3-3.2 (m, 2H), 2.34 (s, 3H), 2.3-1.8 (m, 2H), 1.95 (s, 3H), 0.97 (t, $J=7.0\text{Hz}$, 3H);
TLC : Rf 0.5 (chloroform:methanol=4:1).

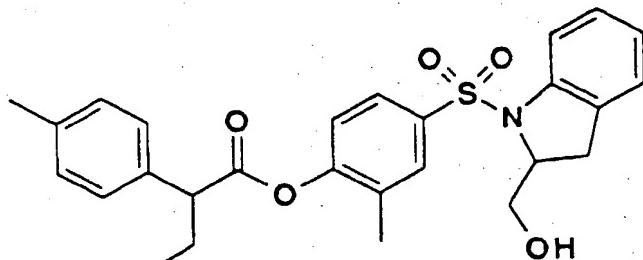
Example 2(72)

4-(2RS-hydroxymethylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester

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NMR (DMSO-d₆): δ 7.61 (1H, s-like), 7.51-7.40 (2H, m), 7.27-6.96 (8H, m), 5.04 (1H, t-like), 4.34 (1H, m), 3.81 (1H, t, J=7Hz), 3.67-3.57 and 3.48-3.39 (each 1H, m), 2.83-2.68 (2H, m), 2.29 (3H, s), 2.20-1.97 and 1.88-1.67 (each 1H, m), 1.86 (3H, s), 0.87 (3H, t, J=7Hz);

TLC : Rf 0.30 (hexane:ethyl acetate=2:1).

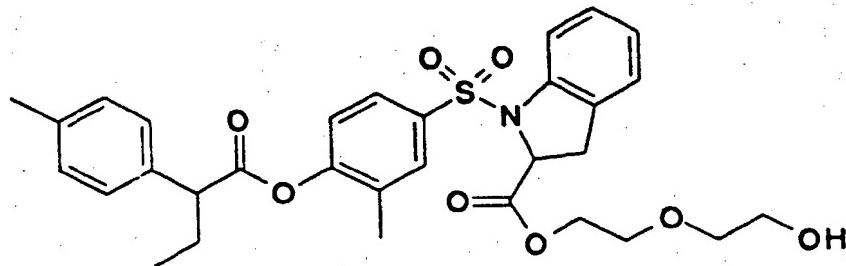
Example 2(73)

25

4-(2RS-(2-(2-hydroxyethoxy)ethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester

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NMR (CDCl₃): δ 7.7-7.5 (m, 3H), 7.3-6.9 (m, 8H), 4.9-4.7 (m, 1H), 4.4-4.3 (m, 2H), 3.8-3.5 (m, 7H), 3.4-3.0 (m, 2H), 2.34 (s, 3H), 2.4-1.8 (m, 2H), 1.93 (s, 3H), 0.97 (t, J=7.2Hz, 3H);

TLC : Rf 0.25 (hexane:ethyl acetate=1:1).

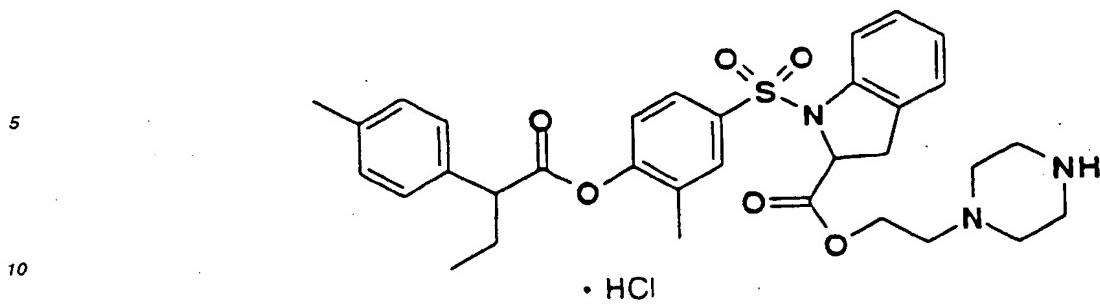
Example 2(74)

45

4-(2RS-(2-(piperazin-4-yl)ethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester · hydrochloride

50

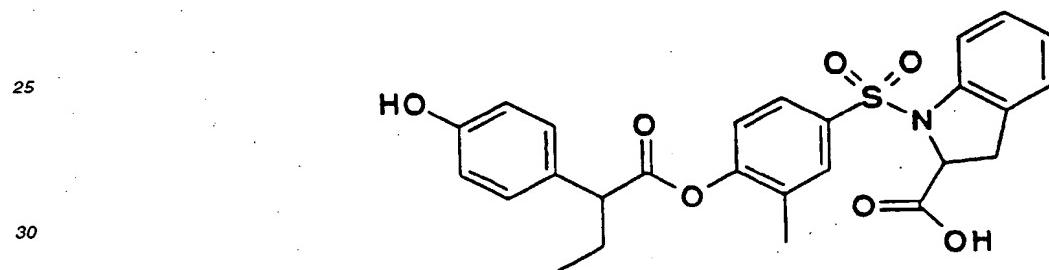
55



15 NMR (CDCl_3): δ 7.7-7.5 (m, 3H), 7.5-7.4 (m, 1H), 7.3-6.9 (m, 7H), 5.2-5.0 (m, 1H), 4.7-4.5 (m, 2H), 4.0-3.5 (m, 11H), 3.4-3.0 (m, 2H), 2.30 (s, 3H), 2.4-2.0 (m, 1H), 1.88 (s, 3H), 2.0-1.8 (m, 1H), 0.93 (t, $J=7.2\text{Hz}$, 3H);
TLC : Rf 0.3 (chloroform:methanol=2:1).

Example 2(75)

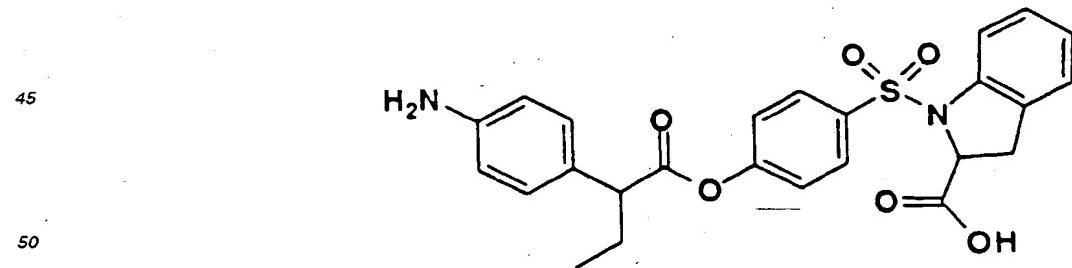
20 4-(2RS-carboxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-hydroxyphenyl)butanoic acid ester



35 NMR (CDCl_3): δ 7.7-7.5 (3H, m), 7.3-7.1 (3H, m), 7.1-6.9 (3H, m), 6.80 (2H, d, $J=8.4\text{Hz}$), 4.8-4.7 (1H, m), 3.7-3.3 (1H, m), 3.3-3.1 (2H, m), 2.3-2.0 (1H, m), 2.0-1.8 (1H, m), 1.91 (3H, s), 0.96 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.42 (chloroform:methanol:water=8:2:0.2).

Example 2(76)

40 4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(4-aminophenyl)butanoic acid ester



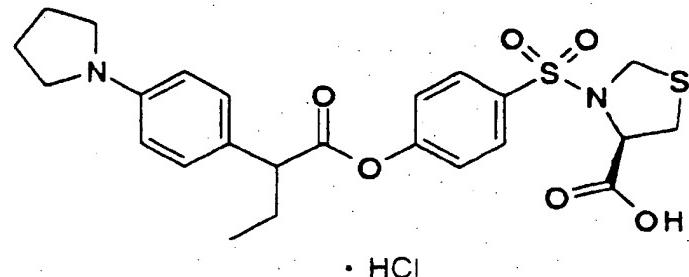
55 NMR (DMSO-d_6): δ 7.83 (2H, d, $J=8.4\text{Hz}$), 7.30 (1H, d, $J=8.2\text{Hz}$), 7.12 (2H, d, $J=8.4\text{Hz}$), 6.97 (2H, d, $J=8.4\text{Hz}$), 7.17-6.90 (3H, m), 6.53 (2H, d, $J=8.4\text{Hz}$), 4.80-4.73 (1H, m), 3.54 (1H, t, $J=7.6\text{Hz}$), 3.25-2.93 (2H, m), 2.09-1.90 (1H, m), 1.78-1.60 (1H, m), 0.86 (3H, t, $J=7.2\text{Hz}$);
TLC : Rf 0.20 (chloroform:methanol:acetic acid=40:2:1).

Example 2(77)

4-(4S-carboxyperhydrothiazol-3-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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NMR (CDCl_3): δ 7.85 (2H, d, $J=8.8\text{Hz}$), 7.21 (2H, d, $J=8.8\text{Hz}$), 7.17 (2H, d, $J=8.8\text{Hz}$), 6.57 (2H, d, $J=8.8\text{Hz}$), 4.83 (1H, dd, $J=7.0$ and 3.4Hz), 4.67 (1H, d, $J=9.0\text{Hz}$), 4.40 (1H, d, $J=9.0\text{Hz}$), 3.59 (1H, t, $J=7.6\text{Hz}$), 3.40-3.18 (5H, m), 3.01 (1H, dd, $J=11.4$ and 7.0Hz), 2.30-2.05 and 2.05-1.75 (each 1H, m), 2.10-1.95 (4H, m), 0.98 (3H, t, $J=7.6\text{Hz}$);
TLC : Rf 0.36 (acetic acid:methanol:chloroform=1:2:40).

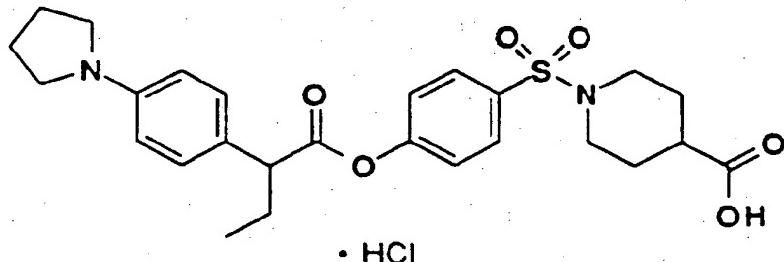
Example 2(78)

25

4-(4-carboxypiperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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NMR (CDCl_3): δ 7.71 (2H, d, $J=8.8\text{Hz}$), 7.21 (2H, d, $J=8.8\text{Hz}$), 7.17 (2H, d, $J=8.8\text{Hz}$), 6.55 (2H, d, $J=8.8\text{Hz}$), 3.72-3.54 (2H, m); 3.59 (1H, t, $J=7.6\text{Hz}$), 3.36-3.20 (4H, m), 2.45 (2H, t-like) 2.38-1.70 (7H, m), 2.08-1.94 (4H, m), 0.98 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.34 (acetic acid:methanol:chloroform=1:2:40).

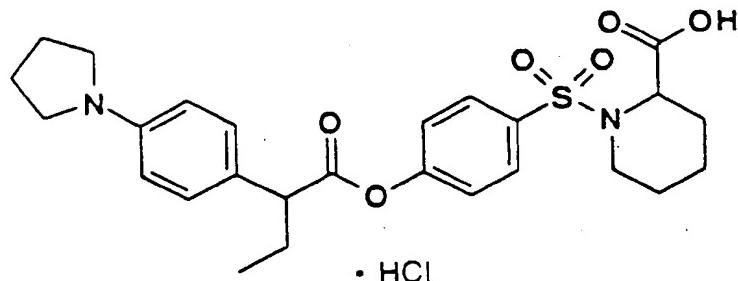
45

Example 2(79)

4-(2RS-carboxypiperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

50

55

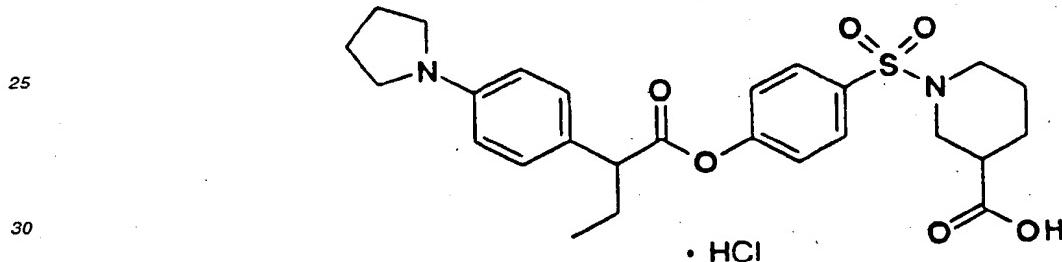


15 NMR (CDCl_3): δ 7.75 (2H, d, $J=8.8\text{Hz}$), 7.21 (2H, d, $J=8.8\text{Hz}$), 7.08 (2H, d, $J=8.8\text{Hz}$), 6.55 (2H, d, $J=8.8\text{Hz}$),
4.8-4.7 (1H, m), 3.8-3.7 (1H, m), 3.58 (1H, t, $J=7.5\text{Hz}$), 3.4-3.1 (5H, m), 2.3-1.2 (12H, m), 0.97 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.48 (acetic acid:methanol:chloroform=1:2:50).

Example 2(80)

4-(3RS-carboxypiperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

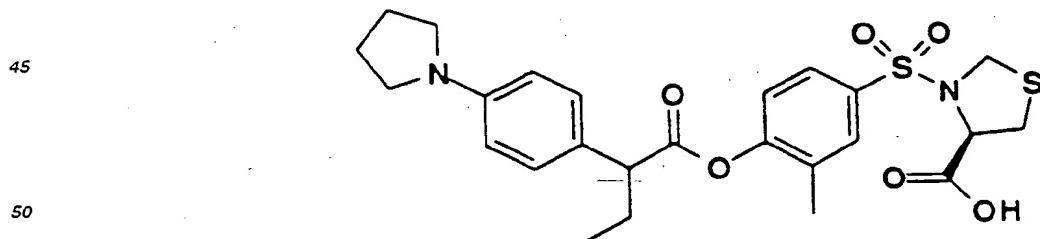
20



35 NMR (CDCl_3): δ 7.75 (2H, d, $J=8.4\text{Hz}$), 7.7-7.3 (4H, m), 7.19 (2H, d, $J=8.4\text{Hz}$), 4.0-3.4 (8H, m), 2.7-2.5 (2H, m),
2.5-2.1 (5H, m), 2.1-1.3 (5H, m), 1.00 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.32 (acetic acid:methanol:chloroform=1:2:100).

Example 2(81)

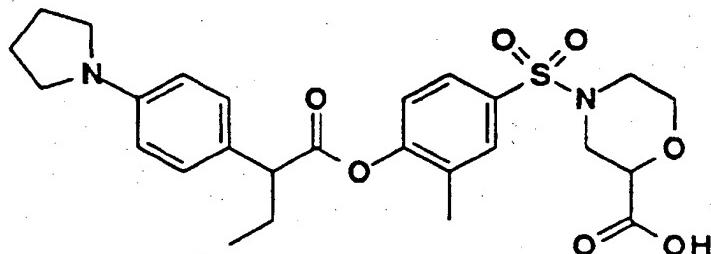
40 4-(4S-carboxyperhydrothiazol-3-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



55 NMR ($\text{CDCl}_3+\text{CD}_3\text{OD}$): δ 7.69 (1H, s), 7.66 (1H, d, $J=8.0\text{Hz}$), 7.21 (2H, d, $J=8.6\text{Hz}$), 7.07 (1H, d, $J=8.0\text{Hz}$), 6.55
(2H, d, $J=8.6\text{Hz}$), 4.71 (1H, dd, $J=7.2, 3.2\text{Hz}$), 4.63 (1H, d, $J=9.8\text{Hz}$), 4.45 (1H, d, $J=9.8\text{Hz}$), 3.61 (1H, t, $J=7.7\text{Hz}$),
3.4-3.2 (5H, m), 2.84 (1H, dd, $J=11.2, 7.2\text{Hz}$), 2.3-2.1 (1H, m), 2.1-1.8 (4H, br), 2.02 (3H, s), 0.98 (3H, d, $J=7.3\text{Hz}$);
TLC : Rf 0.55 (chloroform:methanol:acetic acid=25:5:1).

Example 2(82)

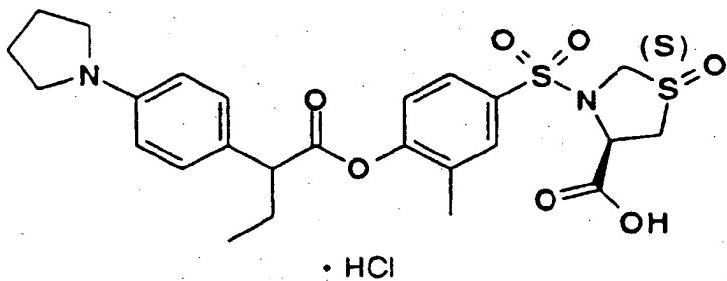
4-(2RS-carboxymorpholin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



NMR (CD_3OD): δ 7.65-7.54 (2H, m), 7.20 (2H, d, $J=8\text{Hz}$), 7.15 (1H, d, $J=8\text{Hz}$), 6.58 (2H, d, $J=8\text{Hz}$), 4.03-3.80 (3H, m), 3.71-3.38 (3H, m), 3.37-3.15 (4H, m), 2.50-1.78 (11H, m), 0.97 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.25 (methanol:chloroform=3:17).

Example 2(83)

4-(1S-oxo-4S-carboxyperhydrothiazol-3-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



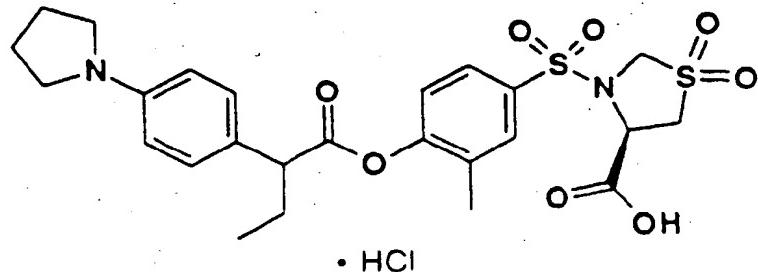
NMR (CD_3OD): δ 7.90-7.75 (2H, m), 7.61 (4H, s), 7.18 (1H, d, $J=8.5\text{Hz}$), 5.25 (1H, dd, $J=8.5, 2.0\text{Hz}$), 5.19 (1H, d, $J=12.0\text{Hz}$), 4.13 (1H, d, $J=12.0\text{Hz}$), 3.98 (1H, t, $J=7.5\text{Hz}$), 3.85-3.70 (4H, m), 3.41 (1H, dd, $J=14.5, 2.0\text{Hz}$), 3.03 (1H, dd, $J=14.5, 8.5\text{Hz}$), 2.35-2.20 (4H, m), 2.40-1.80 (2H, m), 2.04 (3H, s), 1.00 (3H, t, $J=7.5\text{Hz}$);
TLC : Rf 0.18 (chloroform:methanol:acetic acid=40:10:1).

Example 2(84)

4-(4S-carboxy-1,1-dioxoperhydrothiazol-3-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

50

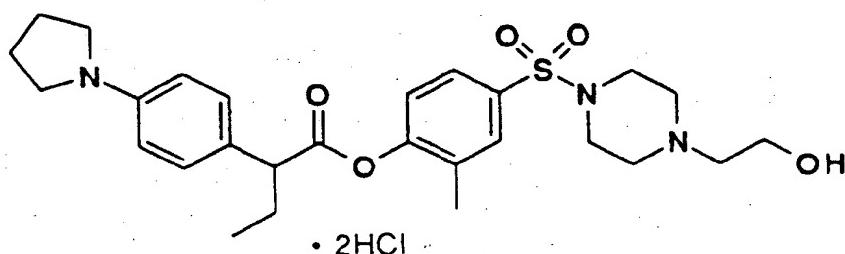
55



15 NMR (CDCl_3): δ 7.75-7.65 (2H, m), 7.48 (4H, s), 7.10 (1H, d, $J=8.5\text{Hz}$), 5.06 (1H, dd, $J=8.5, 4.0\text{Hz}$), 4.68 (1H, d, $J=11.0\text{Hz}$), 4.26 (1H, d, $J=11.0\text{Hz}$), 3.78 (1H, t, $J=7.5\text{Hz}$), 3.70-3.55 (4H, m), 3.55-3.35 (2H, m), 2.40-2.25 (4H, m), 2.40-1.80 (2H, m), 2.07 (3H, s), 1.01 (3H, t, $J=7.5\text{Hz}$);
TLC : Rf 0.14 (chloroform:methanol:acetic acid=40:10:1).

Example 2(85)

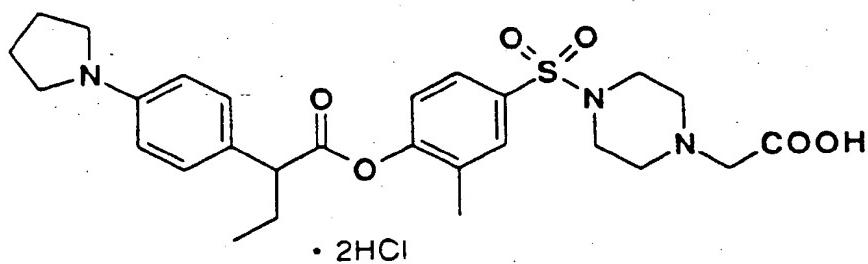
20 4-(4-(2-hydroxyethyl)piperazin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
2hydrochloride



35 NMR (CD_3OD): δ 7.75-7.47 (6H, m), 7.23 (1H, d, $J=8.8\text{Hz}$), 4.03-3.79 (5H, m), 3.79-3.57 (6H, m), 3.40-3.14 (4H, m), 2.77 (2H, t-like, $J=13.8\text{Hz}$), 2.38-2.15 (5H, m), 2.06 (3H, s), 2.15-1.84 (1H, m), 1.00 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.21 (hexane:ethyl acetate=1:1).

40 Example 2(86)

45 4-(4-carboxymethylpiperazin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
2hydrochloride

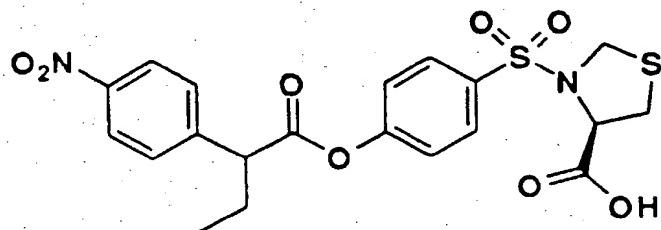


NMR (CD_3OD): δ 7.79-7.53 (6H, m), 7.24 (1H, d, $J=8.0\text{Hz}$), 4.14 (2H, s), 4.00 (1H, t, $J=7.8\text{Hz}$), 3.87-3.70 (4H, m), 3.52 (8H, brs), 2.44-2.15 (5H, m), 2.07 (3H, s), 2.15-1.82 (1H, m), 1.00 (3H, t, $J=7.2\text{Hz}$);

TLC : Rf 0.63 (chloroform:methanol:acetic acid=15:2:1).

Example 2(87)

5 4-(4S-carboxyperhydrothiazol-3-ylsulfonyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester

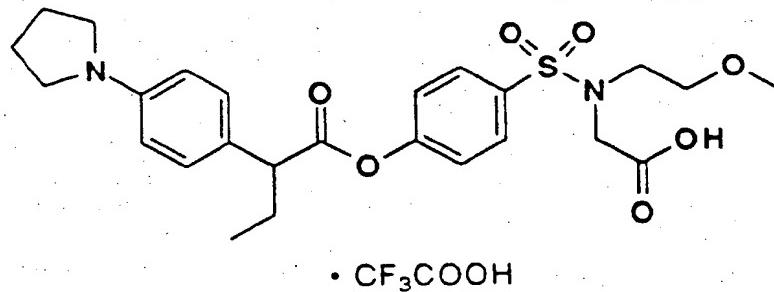


²⁰ NMR (CDCl_3): δ 8.27 (2H, d, $J=8.8\text{Hz}$), 7.94 (2H, d, $J=8.8\text{Hz}$), 7.68 (2H, d, $J=8.8\text{Hz}$), 7.26 (2H, d, $J=8.8\text{Hz}$), 4.86 (1H, dd, $J=3.6$ and 7.4Hz), 4.73 (1H, d, $J=8.0\text{Hz}$), 4.41 (1H, d, $J=8.0\text{Hz}$), 4.03 (1H, t, $J=7.6\text{Hz}$), 3.17 (1H, dd, $J=11.5$ and 3.6Hz), 2.93 (1H, dd, $J=11.5$ and 7.4Hz), 2.40-2.15 and 2.10-1.85 (each 1H, m), 1.00 (3H, t, $J=7.2\text{Hz}$);

TLC : Rf 0.38 (acetic acid:methanol:chloroform=1:2:40).

Example 2(88)

25 4-(N-carboxymethyl-N-2-methoxyethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · trifluoroacetate

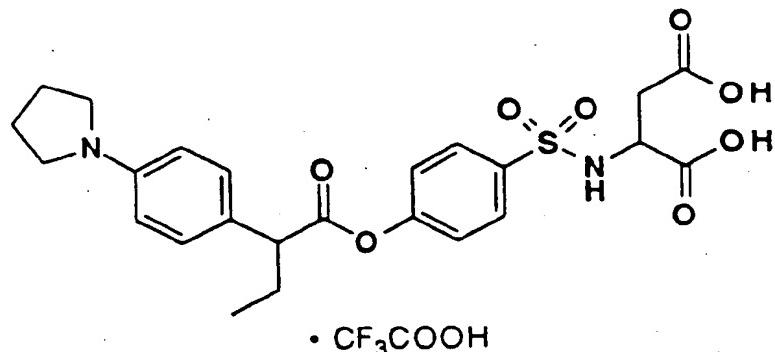


NMR (CD_3OD): δ 7.85 (2H, d, $J=8.6\text{Hz}$), 7.41 (2H, d, $J=8.6\text{Hz}$), 7.17 (2H, d, $J=8.6\text{Hz}$), 7.11 (2H, d, $J=8.6\text{Hz}$), 4.10 (2H, s), 3.77 (1H, t, $J=6.0\text{Hz}$), 3.46 (8H, m), 3.20 (3H, s), 2.20 (1H, m), 2.15 (4H, m), 1.90 (1H, m), 0.97 (3H, t, $J=7.0\text{Hz}$);

TLC : Rf 0.32 (chloroform:methanol:water=9:1:0.1).

Example 2(89)

4-(N-1RS,2-dicarboxyethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · trifluoroacetate

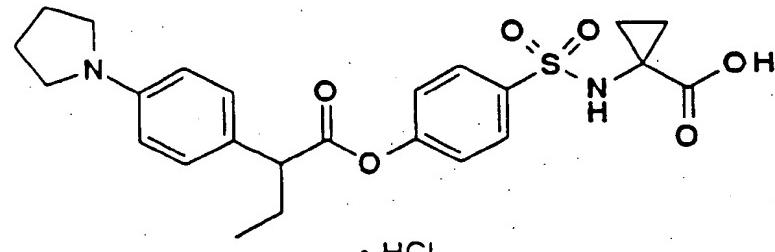


15 NMR (CD₃OD): δ 7.87 (2H, d, J=8.6Hz), 7.36 (2H, brd, J=8.6Hz), 7.14 (2H, d, J=8.6Hz), 7.00 (2H, brd, J=8.6Hz),
 4 21 (1H, t, J=6.0Hz), 3.74 (1H, m), 3.48 (4H, m), 2.72 (2H, d, J=6.2Hz), 2.18 (1H, m), 2.13 (4H, m), 1.87 (1H, m), 0.97
 (3H, t, J=7.4Hz);

TLC : R_f 0.26 (chloroform:methanol:water=9:1:0.1).

20 Example 2(90)

4-(N-(1-carboxycydobutane)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



35 NMR (CDCl₃): δ 7.81 (2H, d, J=8.8Hz), 7.15 (2H, d, J=8.8Hz), 7.05 (2H, d, J=8.8Hz), 6.55 (2H, d, J=8.8Hz), 5.66
 (1H, s), 3.58 (1H, t, J=7.6Hz), 3.36-3.18 (4H, t-like), 2.30-2.00 and 2.00-1.75 (each 1H, m), 2.06-1.96 (4H, m), 1.56-1.35
 (4H, m), 0.97 (3H, t, J=7.4Hz);

40 TLC : R_f 0.38 (acetic acid:methanol:chloroform=1:2:40).

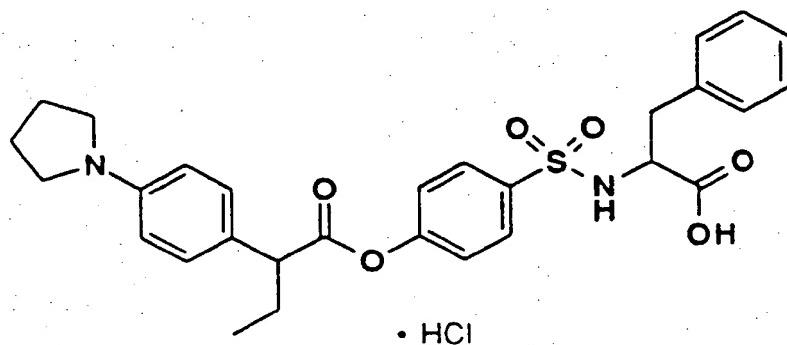
Example 2(91)

4-(N-1RS-carboxy-2-phenylethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

45

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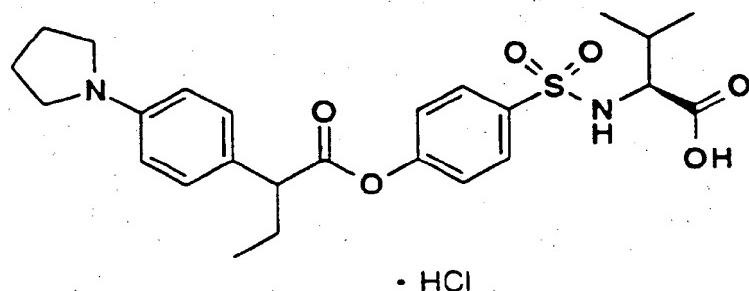
15 NMR (DMSO-d₆): δ 8.38 (1H, d, J=10Hz), 7.55 (2H, d, J=9Hz), 7.30-7.00 (9H, m), 6.76 (2H, d, J=9Hz), 3.95-3.79 (1H, m), 3.71 (1H, t, J=7Hz), 3.40-3.20 (4H, m), 2.94 (1H, dd, J=15Hz, 5Hz), 2.70 (1H, dd, J=15Hz, 8Hz), 2.20-1.90 (5H, m), 1.90-1.65 (1H, m), 0.90 (3H, t, J=7Hz);

TLC : Rf 0.19 (ethyl acetate:hexane:acetic acid=5:5:0.1).

20 Example 2(92)

4-(N-1S-carboxy-2-methylpropylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

25



40 NMR (DMSO-d₆): δ 8.05 (1H, d, J=9Hz), 7.78 (2H, d, J=8Hz), 7.25 (2H, d, J=8Hz), 7.17 (2H, d, J=8Hz), 6.86-6.70 (2H, m), 3.73 (1H, t, J=7Hz), 3.50 (1H, dd, J=9Hz, 6Hz), 3.38-3.20 (4H, m), 2.20-1.68 (7H, m), 0.88 (3H, t, J=7Hz), 0.80 (3H, d, J=7Hz), 0.76 (3H, d, J=7Hz);

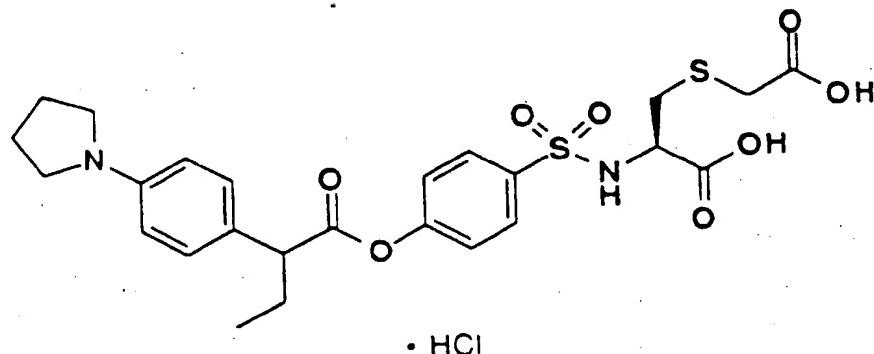
TLC : Rf 0.34 (ethyl acetate).

45 Example 2(93)

4-(N-(1S-carboxy-2-carboxymethylthioethyl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

50

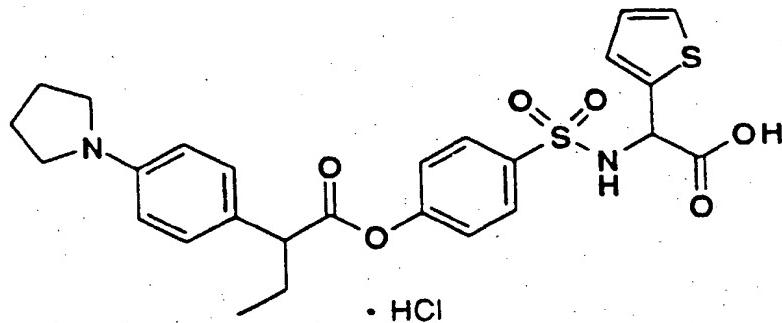
55



NMR (CD_3OD): δ 7.89 (2H, d, $J=8.8\text{Hz}$), 7.63 (2H, d, $J=15.0\text{Hz}$), 7.62 (2H, d, $J=15.0\text{Hz}$), 7.18 (2H, d, $J=8.8\text{Hz}$), 4.08 (1H, dd, $J=5.9, 7.5\text{Hz}$), 3.91 (1H, t, $J=7.5\text{Hz}$), 3.82-3.70 (4H, m), 3.19 (2H, s), 3.00 (1H, dd, $J=5.9, 14.0\text{Hz}$), 2.84 (1H, dd, $J=7.5, 14.0\text{Hz}$), 2.40-2.12 (5H, m), 2.02-1.80 (1H, m), 0.98 (3H, t, $J=7.0\text{Hz}$);
TLC : R_f 0.20 (chloroform:methanol:water=7:3:0.3).

Example 2(94)

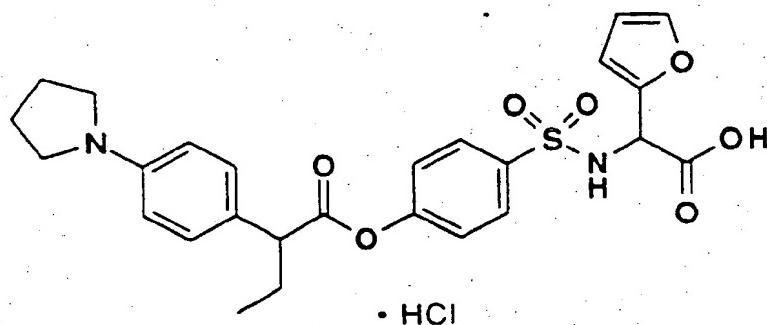
4-(N-1RS-carboxy-1-(thiophen-2-yl)methylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



NMR (DMSO-d_6): δ 8.88 (1H, d, $J=9.0\text{Hz}$), 7.77 (2H, d, $J=8.8\text{Hz}$), 7.40 (1H, dd, $J=1.2, 5.0\text{Hz}$), 7.24 (2H, d, $J=8.4\text{Hz}$), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.00-6.91 (1H, m), 6.88 (1H, dd, $J=3.7, 5.0\text{Hz}$), 6.85-6.72 (2H, m), 5.16 (1H, d, $J=9.0\text{Hz}$), 3.71 (1H, t, $J=7.2\text{Hz}$), 3.40-3.20 (4H, m), 2.20-1.90 (5H, m), 1.88-1.70 (1H, m), 0.89 (3H, t, $J=7.2\text{Hz}$);
TLC : R_f 0.27 (chloroform:methanol:water=4:1:0.1).

Example 2(95)

4-(N-1RS-carboxy-1-(furan-2-yl)methylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

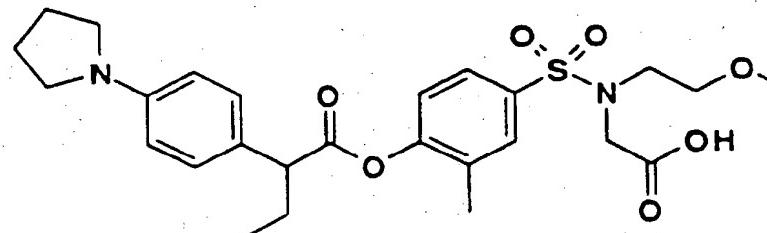


15 NMR (DMSO-d₆): δ 8.78 (1H, d, J=9.0Hz), 7.75 (2H, d, J=8.6Hz), 7.46 (1H, m), 7.24 (2H, d, J=8.2Hz), 7.12 (2H, d, J=8.6Hz), 6.90-6.70 (2H, m), 6.31-6.24 (1H, m), 6.19 (1H, d, J=2.8Hz), 5.02 (1H, d, J=9.0Hz), 3.71 (1H, t, J=7.6Hz), 3.40-3.20 (4H, m), 2.20-1.86 (5H, m), 1.86-1.68 (1H, m), 0.89 (3H, t, J=7.4Hz);
TLC : Rf 0.27 (chloroform:methanol:water=4:1:0.1).

20 Example 2(96)

4-(N-carboxymethyl-N-2-methoxyethylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

25

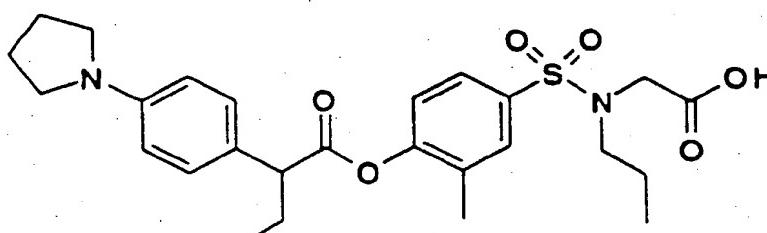


40 NMR (CDCl₃): δ 7.64 (1H, d, J=2.0Hz), 7.61 (1H, dd, J=8.0, 2.0Hz), 7.21 (2H, d, J=8.5Hz), 7.04 (1H, d, J=8.0Hz), 6.55 (2H, d, J=8.5Hz), 4.08 (2H, s), 3.61 (1H, t, J=7.5Hz), 3.55 (2H, t, J=4.5Hz), 3.40 (2H, t, J=4.5Hz), 3.35-3.20 (4H, m), 3.29 (3H, s), 2.30-1.70 (2H, m), 2.05-1.95 (4H, m), 2.01 (3H, s), 0.99 (3H, t, J=7.5Hz);
TLC : Rf 0.47 (chloroform:methanol:acetic acid=40:2:1).

Example 2(97)

45 4-(N-propyl-N-carboxymethylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

45



NMR (CDCl₃): δ 7.70-7.55 (2H, m), 7.23 (2H, d, J=8Hz), 7.01 (1H, d, J=8Hz), 6.55 (2H, d, J=8Hz), 4.20-3.80 (1H,

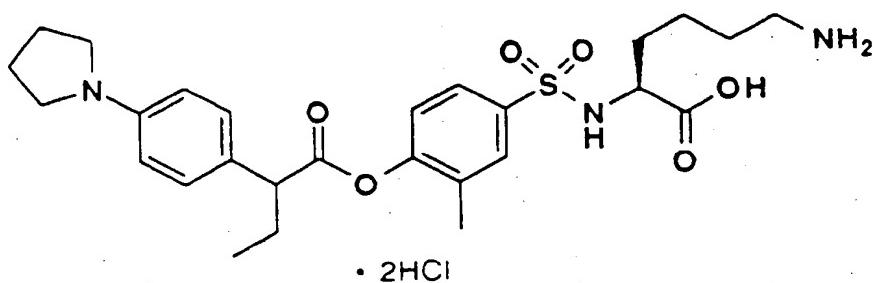
EP 0 769 498 A1

br), 3.98 (2H, s), 3.60 (1H, t, $J=7\text{Hz}$), 3.35-3.07 (6H, m), 2.28-1.75 (9H, m), 1.60-1.38 (2H, m), 0.98 (3H, t, $J=7\text{Hz}$), 0.90 (3H, t, $J=7\text{Hz}$);

TLC : Rf 0.23 (chloroform:methanol=19:1).

5 Example 2(98)

4-(N-1S-carboxy-5-aminopentylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
2hydrochloride

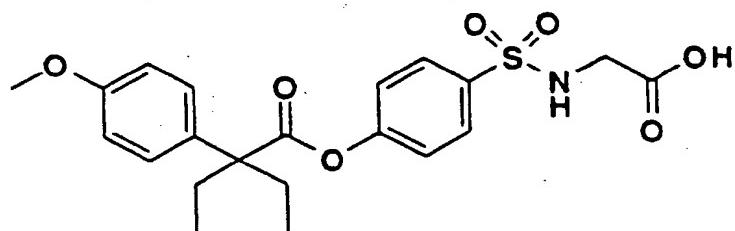


NMR (CD_3OD): δ 7.80-7.47 (6H, m), 7.10 (1H, d, $J=8\text{Hz}$), 3.95 (1H, t, $J=7\text{Hz}$), 3.90-3.68 (5H, m), 2.95-2.80 (2H, m), 2.35-2.20 (5H, m), 2.10-1.85 (1H, m), 1.99 (3H, s), 1.85-1.30 (6H, m), 0.98 (3H, t, $J=7\text{Hz}$);

TLC : Rf 0.22 (chloroform:methanol:water=8:2:0.1).

Example 2(99)

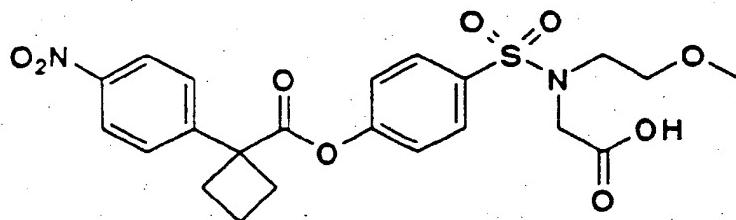
4-(N-carboxymethylsulfamoyl)phenyl 2-(4-methoxyphenyl)-2-ethylbutanoic acid ester



NMR (CDCl_3): δ 7.80 (2H, d, $J=8.8\text{Hz}$), 7.25 (2H, d, $J=8.8\text{Hz}$), 7.04 (2H, d, $J=8.6\text{Hz}$), 6.90 (2H, d, $J=8.8\text{Hz}$), 3.80 (3H, s), 3.73 (2H, brs), 2.25-2.00 (4H, m), 0.82 (6H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.10 (hexane:ethyl acetate=2:1).

Example 2(100)

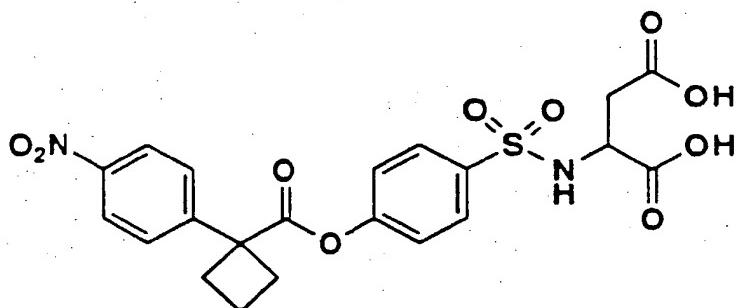
4-(N-2-methoxyethyl-N-carboxymethylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester



NMR (CDCl_3): δ 8.25 (2H, d, $J=9.0\text{Hz}$), 7.82 (2H, d, $J=9.0\text{Hz}$), 7.55 (2H, d, $J=9.0\text{Hz}$), 7.11 (2H, d, $J=9.0\text{Hz}$), 4.13 (2H, s), 3.53 (2H, t, $J=5.0\text{Hz}$), 3.41 (2H, t, $J=5.0\text{Hz}$), 3.27 (3H, s), 3.06 (2H, m), 2.67 (2H, m), 2.26 (1H, m), 2.04 (1H, m);
TLC : Rf 0.29 (chloroform:methanol:water=9:1:0.1).

15

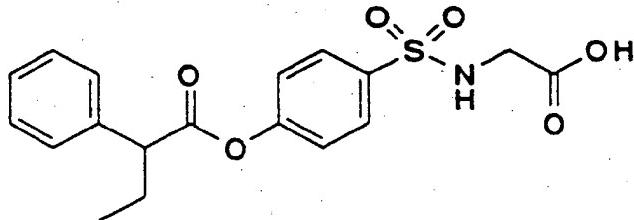
Example 2(101)

20
4-(N-1RS,2-dicarboxyethylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester

NMR (CD_3OD): δ 8.27 (2H, d, $J=8.8\text{Hz}$), 7.87 (2H, d, $J=8.8\text{Hz}$), 7.65 (2H, d, $J=8.8\text{Hz}$), 7.15 (2H, d, $J=8.8\text{Hz}$),
35 4.21 (1H, t, $J=5.8\text{Hz}$), 3.05 (2H, m), 2.71 (4H, m), 2.25 (1H, m), 2.04 (1H, m);
TLC : Rf 0.17 (chloroform:methanol:water=8:2:0.2).

Example 2(102)

40 4-(N-carboxymethylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester



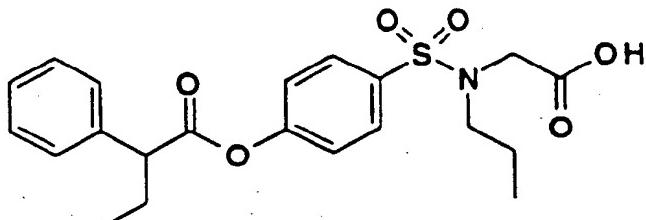
NMR (DMSO-d_6): δ 8.04 (1H, brs), 7.82 (2H, d, $J=8\text{Hz}$), 7.45-7.25 (5H, m), 7.21 (2H, d, $J=8\text{Hz}$), 3.86 (1H, t, $J=7\text{Hz}$), 3.56 (2H, s), 2.10 and 1.85 (each 1H, m), 0.91 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.32 (acetic acid:methanol:chloroform=1:3:30).

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Example 2(103)

4-(N-propyl-N-carboxymethylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester

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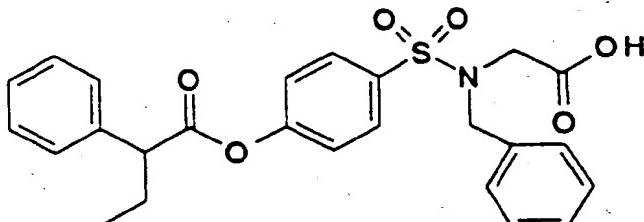
NMR (DMSO-d₆): δ 12.65 (1H, brs), 8.04 (1H, brs), 7.84 (2H, d, J=8Hz), 7.45-7.25 (5H, m), 7.21 (2H, d, J=8Hz), 3.92 (2H, s), 3.85 (1H, t, J=7Hz), 3.10 (2H, t), 2.10 and 1.86 (each 1H, m), 1.44 (2H, m), 0.92 (3H, t, J=7Hz), 0.77 (3H, t, J=7Hz);

15 TLC : Rf 0.54 (acetic acid:methanol:chloroform=1:3:30).

Example 2(104)

20 4-(N-benzyl-N-carboxymethylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester

25



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NMR (CDCl₃): δ 7.90-7.79 (2H, m), 7.43-7.08 (12H, m), 6.34 (1H, br), 4.46 (2H, s), 3.90 (2H, s), 3.70 (1H, t, J=7Hz), 2.22 (1H, ddq, J=14Hz, 7Hz, 7Hz), 1.92 (1H, ddq, J=14Hz, 7Hz, 7Hz), 0.98 (3H, t, J=7Hz);

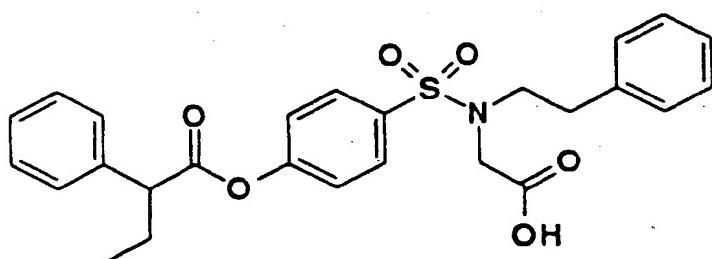
TLC : Rf 0.42 (dichloromethane:methanol=9:1).

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Example 2(105)

40 4-(N-2-phenylethyl-N-carboxymethylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester

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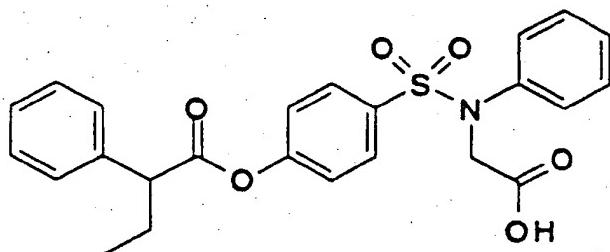
NMR (CDCl₃): δ 7.77 (2H, d, J=8Hz), 7.40-7.04 (12H, m), 5.89 (1H, br), 3.95 (2H, s), 3.69 (1H, t, J=7Hz), 3.53-3.40 (2H, m), 2.91-2.80 (2H, m), 2.21 (1H, ddq, J=14Hz, 7Hz, 7Hz), 1.90 (1H, ddq, J=14Hz, 7Hz, 7Hz), 0.97 (3H, t, J=7Hz);

TLC : Rf 0.41 (dichloromethane:methanol=9:1).

55

Example 2(106)

4-(N-phenyl-N-carboxymethylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester



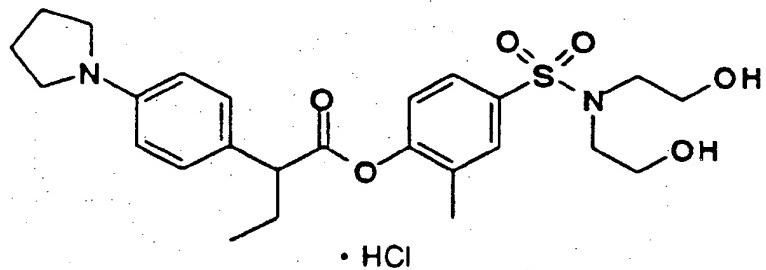
5

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NMR (CDCl_3): δ 7.63 (2H, d, $J=8\text{Hz}$), 7.45-7.04 (12H, m), 6.20 (1H, br), 4.40 (2H, s), 3.70 (1H, t, $J=7\text{Hz}$), 2.23 (1H, ddq, $J=14\text{Hz}, 7\text{Hz}, 7\text{Hz}$), 1.91 (1H, ddq, $J=14\text{Hz}, 7\text{Hz}, 7\text{Hz}$), 0.99 (3H, t, $J=7\text{Hz}$);
TLC : R_f 0.41 (dichloromethane:methanol=9:1).

Example 2(107)

20 4-(N,N-bis(2-hydroxyethyl)sulfamoyl)-2-methyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



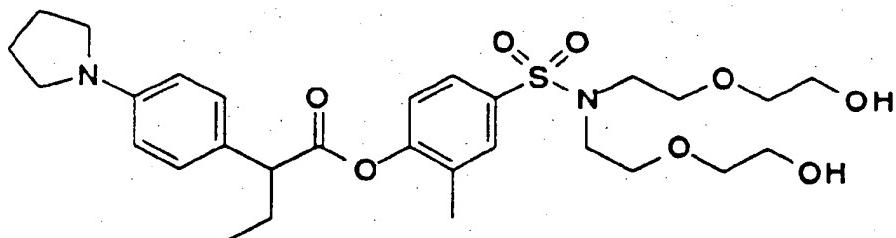
25

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³⁵ NMR (CD_3OD): δ 7.78-7.50 (6H, m), 7.15 (1H, d, $J=8\text{Hz}$), 3.96 (1H, t, $J=7\text{Hz}$), 3.95-3.80 (8H, m), 3.35-3.18 (4H, m), 2.40-2.15 (5H, m), 2.10-1.80 (1H, m), 2.02 (3H, s), 0.99 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.23 (hexane:ethyl acetate=1:1).

Example 2(108)

4-(N,N-bis(2-(2-hydroxyethoxy)ethyl)sulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



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55 NMR (CDCl_3): 8.7.70-7.55 (2H, m), 7.23 (2H, d, $J=9\text{Hz}$), 7.06 (1H, d, $J=8\text{Hz}$), 6.55 (2H, d, $J=9\text{Hz}$), 3.75-3.45 (13H, m), 3.43-3.23 (8H, m), 3.05 (2H, brs), 2.30-1.73 (9H, m), 0.98 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.33 (ethyl acetate).

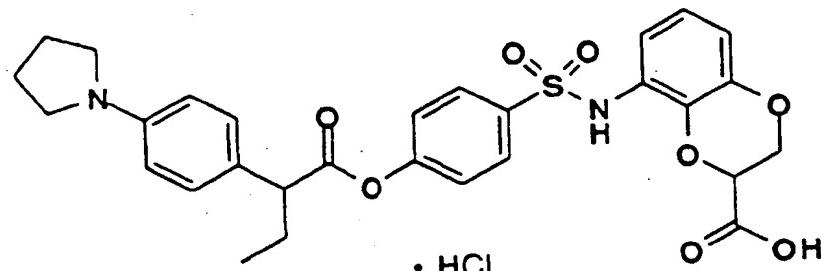
Example 2(109)

4-(N-(3RS-carboxy-1,4-benzodioxan-5-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester hydrochloride

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NMR (DMSO-d₆): δ 9.67 (1H, s), 7.80 (2H, d, J=9Hz), 7.20 (2H, d, J=9Hz), 7.13 (2H, d, J=9Hz), 6.84-6.57 (5H, m), 4.78 (1H, t, J=3Hz), 4.28 (1H, dd, J=11Hz, 3Hz), 4.13-4.00 (1H, m), 3.68 (1H, t, J=7Hz), 3.35-3.18 (4H, m), 2

20 15-1.88 (5H, ml, 1.88-1.60 (1H, m), 0.88 (3H, t, J=7Hz);

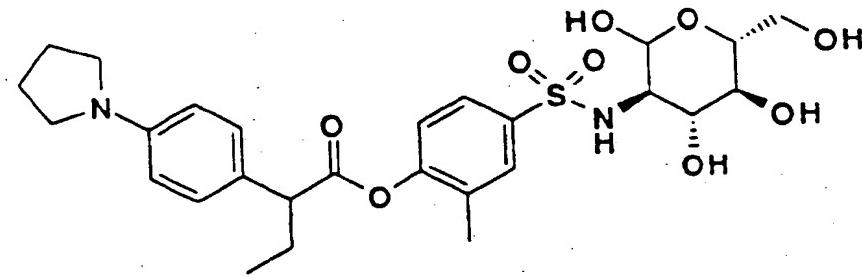
TLC : Rf 0.18 (chloroform:methanol:acetic acid=40:2:1).

Example 2(110)

25 4-(N-2RS-hydroxy-4R-hydroxy-5R-hydroxy-6R-hydroxymethylperhydropyran-3R-ylsulfamoyl)-2-methylphenyl
2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

30

35



40 NMR (DMSO-d₆+3 drop of CD₃OD): δ 7.80-7.60 (2H, m), 7.20 (2H, d, J=8.5Hz), 7.05 (1H, d, J=8.5Hz), 6.60 (2H, d, J=8.5Hz), 4.78 (1H, d, J=3.5Hz), 3.70 (1H, t, J=7.5Hz), 3.65-3.35 (4H, m), 3.30-3.15 (4H, m), 3.03 (1H, t, J=9.0Hz), 2.90 (1H, dd, J=10.5, 3.5Hz), 2.20-1.60 (2H, m), 2.00-1.90 (4H, m), 1.94 (3H, s), 0.91 (3H, t, J=7.5Hz);

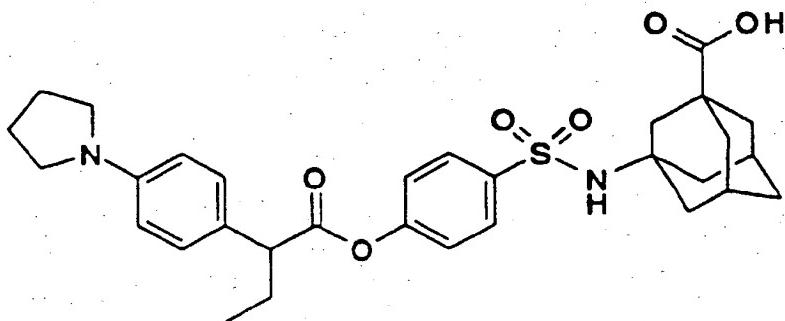
TLC : Rf 0.55 (chloroform:methanol:water=40:10:1).

45 Example 2(111)

4-(N-3-carboxyadamantan-1-ylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

50

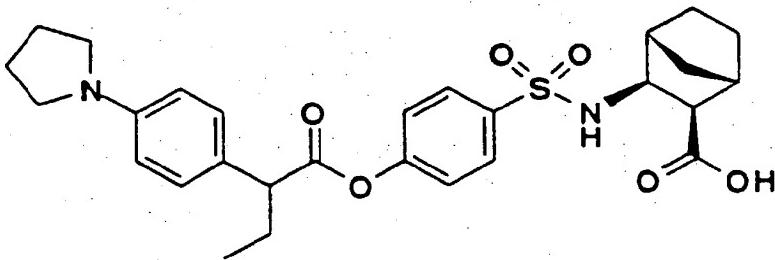
55



15 NMR (CDCl_3): δ 7.85 (2H, d, $J=8.8\text{Hz}$), 7.22 (2H, d, $J=8.8\text{Hz}$), 7.12 (2H, d, $J=8.8\text{Hz}$), 6.54 (2H, d, $J=8.8\text{Hz}$), 4.60 (1H, s), 3.59 (1H, t, $J=7.4\text{Hz}$), 3.40-3.15 (4H, m), 2.30-1.40 (20H, m), 0.98 (3H, t, $J=7.6\text{Hz}$);
TLC : Rf 0.60 (chloroform:methanol:acetic acid=40:2:1).

Example 2(112)

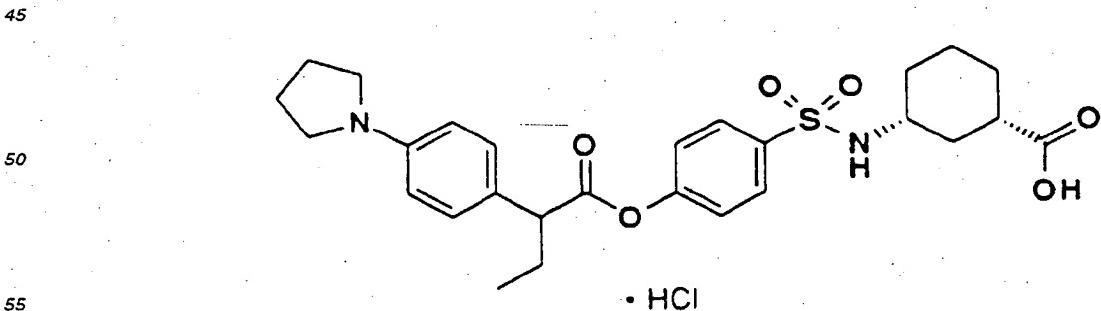
20 4-(N-(1S,4R,3R-carboxybicyclo[2.2.1]heptan-2S-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



35 NMR (CDCl_3): δ 7.83 (2H, d, $J=8.6\text{Hz}$), 7.21 (2H, d, $J=8.6\text{Hz}$), 7.11 (2H, d, $J=8.6\text{Hz}$), 6.55 (2H, d, $J=8.6\text{Hz}$), 7.6-7.4 (1H, br), 3.58 (1H, t, $J=7.6\text{Hz}$), 3.58 (1H, t, $J=8.0\text{Hz}$), 3.40-3.20 (4H, m), 2.64 (1H, d, $J=8.0\text{Hz}$), 2.42 (1H, s), 2.30-1.70 (4H, m), 2.10-1.90 (4H, m), 1.50-1.30 (2H, m), 1.30-0.90 (3H, m), 0.97 (3H, t, $J=7.3\text{Hz}$);
TLC : Rf 0.33 (chloroform:methanol:acetic acid=40:2:1).

Example 2(113)

40 4-(N-3S-carboxycydoxane-1R-ylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



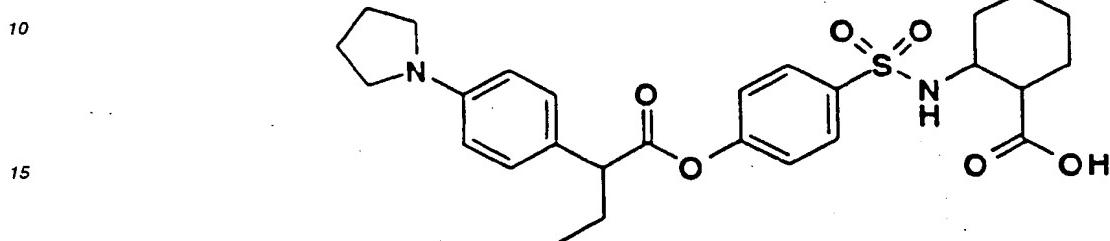
NMR (DMSO-d_6): δ 7.90-7.70 (3H, m), 7.30-7.10 (4H, m), 6.70 (2H, d, $J=9\text{Hz}$), 3.71 (1H, t, $J=7\text{Hz}$), 3.35-3.15 (4H, m), 3.09-2.86 (1H, m), 2.27-1.45 (11H, m), 1.33-0.95 (4H, m), 0.89 (3H, t, $J=7\text{Hz}$);

EP 0 769 498 A1

TLC : Rf 0.36 (ethyl acetate:hexane:acetic acid=5:5:0.1).

Example 2(114)

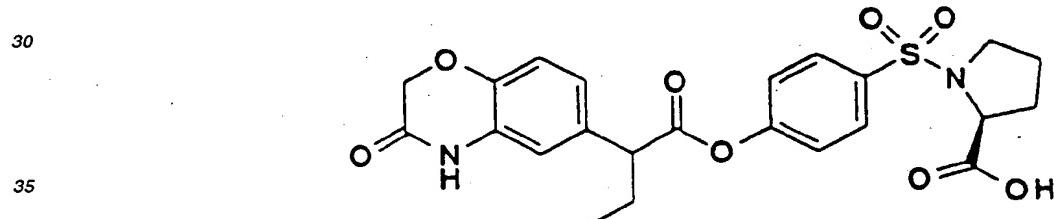
5 4-(N-2RS-carboxycyclohexane-1RS-ylsulfamoylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



20 NMR (CDCl_3): δ 7.84 (2H, d, $J=8.8\text{Hz}$), 7.23-7.08 (4H, m), 6.55 (2H, d, $J=8.6\text{Hz}$), 5.70 (1H, brs), 3.59 (1H, t, $J=8.0\text{Hz}$), 3.45 (1H, brs), 3.32-3.26 (4H, m), 2.65 (1H, brs), 2.25-1.20 (14H, m), 0.98 (3H, t, $J=7.0\text{Hz}$);
TLC : Rf 0.22 (hexane:ethyl acetate=1:1).

Example 2(115)

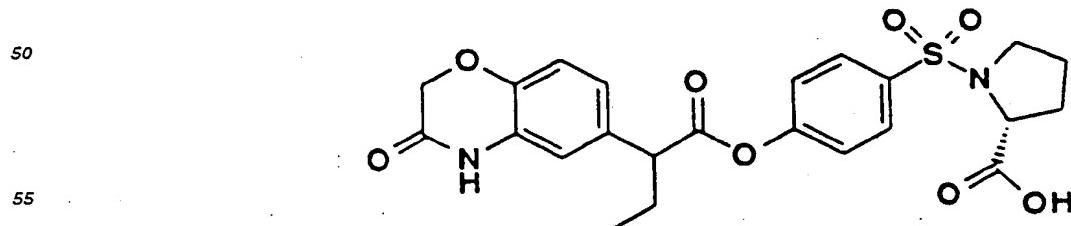
25 4-(2S-carboxypyrrrolidin-1-ylsultonyl)phenyl 2RS-(2H-1,4-benzoxazin-3-on-6-yl)butanoic acid ester



40 NMR (DMSO-d_6): δ 10.73 (1H, s), 7.88 (2H, d, $J=8.6\text{Hz}$), 7.26 (2H, d, $J=8.6\text{Hz}$), 6.95 (3H, s), 4.57 (2H, s), 4.13-4.00 (1H, m), 3.79 (1H, t, $J=7.6\text{Hz}$), 3.40-3.08 (2H, m), 2.20-1.40 (6H, m), 0.91 (3H, t, $J=7.2\text{Hz}$);
TLC : Rf 0.35 (acetic acid:methanol:chloroform=1:2:40).

Example 2(116)

45 4-(2R-carboxypyrrrolidin-1-ylsultonyl)phenyl 2RS-(2H-1,4-benzoxazin-3-on-6-yl)butanoic acid ester



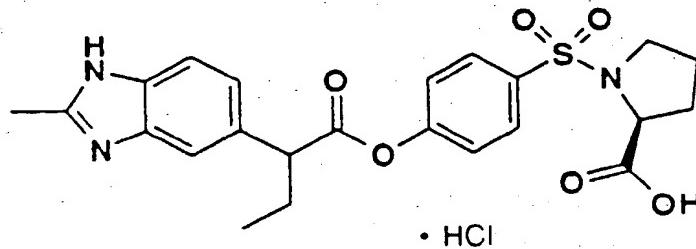
NMR (DMSO-d_6): δ 13.4-12.2 (1H, br), 10.72 (1H, s), 7.88 (2H, d, $J=8.6\text{Hz}$), 7.29 (2H, d, $J=8.6\text{Hz}$), 6.95 (3H, s),

EP 0 769 498 A1

4.57 (2H, s), 4.16-4.08 (1H, m), 3.80 (1H, t, $J=7.6\text{Hz}$), 3.50-3.05 (2H, m), 2.05-1.45 (6H, m), 0.91 (3H, t, $J=7.2\text{Hz}$);
 TLC : Rf 0.36 (acetic acid:methanol:chloroform=1:2:40).

Example 2(117)

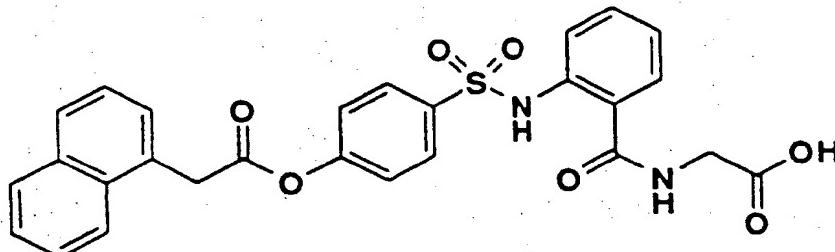
5
 4-(2S-carboxypyrrolidin-1-ylsulfonyl)phenyl 2RS-(2-methylbenzimidazol-5-yl)butanoic acid ester · hydrochloride



20 NMR (CD_3OD): δ 7.90-7.61 (5H, m), 7.23 (2H, d, $J=9\text{Hz}$), 4.23-4.17 (1H, m), 4.06 (1H, t, $J=8\text{Hz}$), 3.51-3.40 (1H, m), 3.31-3.20 (2H, m), 2.87 (3H, s), 2.38-2.24 (1H, m), 2.06-1.86 (3H, m), 1.76-1.64 (1H, m), 1.01 (3H, t, $J=7\text{Hz}$);
 TLC : Rf 0.21 (chloroform:methanol:water=8:2:0.2).

Example 2(118)

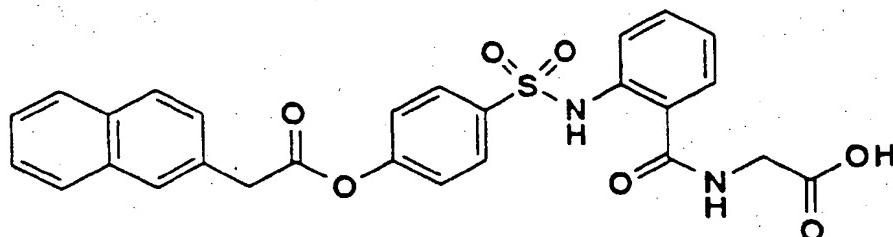
25 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(naphthalen-1-yl)acetic acid ester



40 NMR (DMSO-d_6): δ 12.74 (1H, br), 11.58 (1H, br), 9.20 (1H, t, $J=5\text{Hz}$), 8.08-7.70 (6H, m), 7.63-7.42 (6H, m), 7.29 (2H, d, $J=9\text{Hz}$), 7.17-7.10 (1H, m), 4.46 (2H, s), 3.89 (2H, d, $J=6\text{Hz}$);
 TLC : Rf 0.28 (acetic acid:methanol:chloroform=1:2:40).

Example 2(119)

45 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(naphthalen-2-yl)acetic acid ester

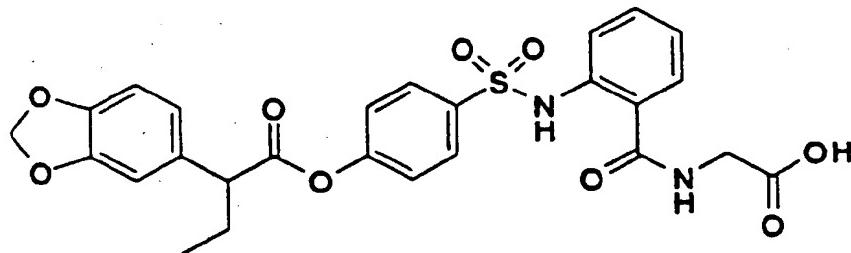


EP 0 769 498 A1

NMR (DMSO-d₆): δ 12.67 (1H, br), 11.63 (1H, br), 9.24 (1H, t-like), 7.93-7.71 (7H, m), 7.54-7.43 (5H, m), 7.36-7.29 (2H, m), 7.18-7.10 (1H, m), 4.15 (2H, s), 3.90 (2H, d, J=6Hz);
TLC : Rf 0.31 (acetic acid:methanol:chloroform=1:2:40).

5 Example 2(120)

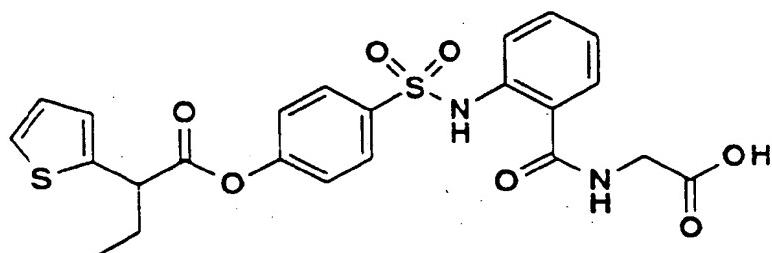
4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(1,3-benzodioxol-5-yl)butanoic acid ester



20 NMR (DMSO-d₆): δ 12.73 (1H, br), 11.62 (1H, br), 9.22 (1H, t, J=6Hz), 7.82-7.71 (3H, m), 7.53-7.42 (2H, m), 7.26-7.10 (3H, m), 6.94-6.79 (3H, m), 6.01 (2H, s), 3.89 (2H, d, J=5Hz), 3.75 (1H, t, J=8Hz), 2.16-1.95 and 1.86-1.64 (each 1H, m), 0.86 (3H, t, J=7Hz);
TLC : Rf 0.68 (acetic acid:methanol:chloroform=1:3:30).

25 Example 2(121)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(thiophen-2-yl)butanoic acid ester



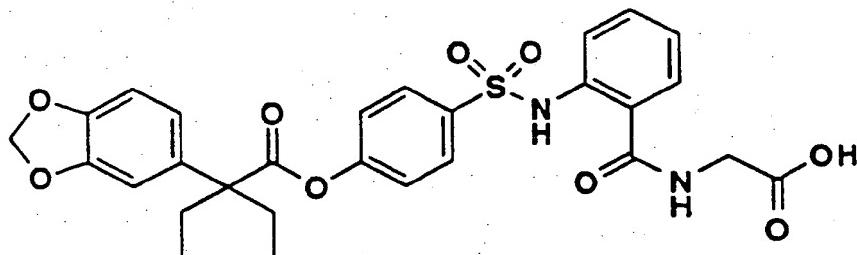
40 NMR (DMSC-d₆): δ 9.4-9.2 (1H, br), 7.9-7.7 (3H, m), 7.6-7.4 (3H, m), 7.3-7.0 (5H, m), 4.19 (1H, t, J=7Hz), 3.90 (2H, d, J=5Hz), 2.2-2.0 (1H, m), 2.0-1.8 (1H, m), 0.92 (3H, t, J=7Hz);
TLC : Rf 0.18 (acetic acid:methanol:chloroform=1:2:40).

45 Example 2(122)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(1,3-benzodioxol-5-yl)-2-ethylbutanoic acid ester

50

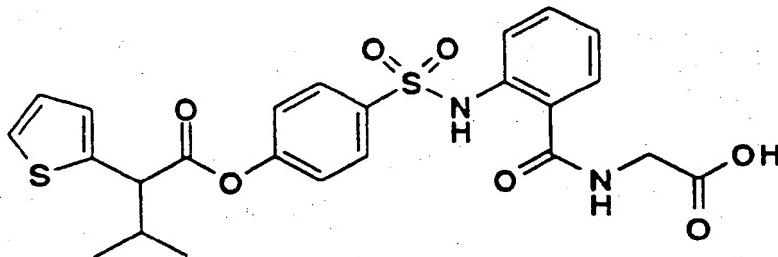
55



NMR (DMSO-d₆): δ 12.62 (1H, br), 11.66 (1H, br), 9.24 (1H, t-like), 7.82-7.71 (3H, m), 7.52-7.42 (2H, m), 7.31-7.10 (3H, m), 6.91-6.76 (3H, m), 6.01 (2H, s), 3.89 (2H, d, J=5Hz), 2.09-1.96 (4H, m), 0.75 (6H, t, J=8Hz);
15 TLC : Rf 0.39 (acetic acid:methanol:chloroform=1:2:40).

Example 2(123)

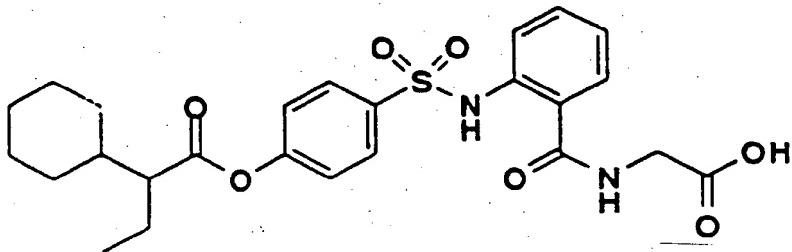
20 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(thiophen-2-yl)-3-methylbutanoic acid ester



35 NMR (DMSO-d₆): δ 12.64 (1H, br), 11.70 (1H, br), 9.24 (1H, t-like), 7.82 (2H, d, J=8Hz), 7.74 (1H, d, J=8Hz), 7.54-7.43 (3H, m), 7.26-7.00 (5H, m), 3.95 (1H, d, J=7Hz), 3.90 (2H, d, J=6Hz), 2.36-2.18 (1H, m), 1.07 and 0.83(each 3H, each d, J=7Hz);
TLC : Rf 0.24 (acetic acid:methanol:chloroform=1:2:40).

Example 2(124)

40 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(cyclohexane-1-yl)butanoic acid ester



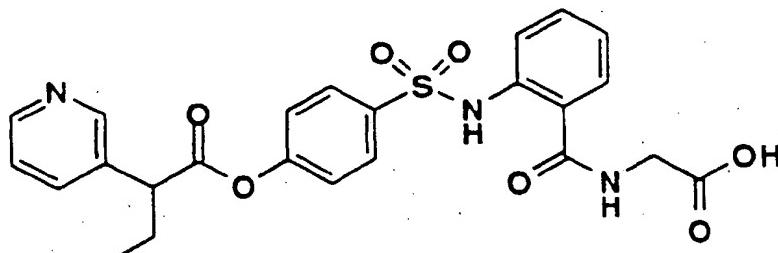
55 NMR (DMSO-d₆): δ 12.72 (1H, br), 11.64 (1H, br), 9.27 (1H, br), 7.83 (2H, d, J=10Hz), 7.75 (1H, d, J=10Hz), 7.51 (1H, t, J=10Hz), 7.48 (1H, t, J=8Hz), 7.27 (2H, d, J=12Hz), 7.15 (1H, J=10Hz), 3.90 (2H, d, J=3Hz), 2.35-2.30 (1H, m), 1.78 (1H, d-like), 1.71-1.55 (7H, ml, 1.25-0.98 (5H, m), 0.92 (3H, t, J=7Hz);
TLC : Rf 0.30 (acetic acid:methanol:chloroform=1:2:20).

Example 2(125)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(pyridin-3-yl)butanoic acid ester

5

10



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NMR (DMSO-d₆): δ 12.00 (2H, br), 9.36 (1H, br), 8.68-8.46 (2H, br), 7.85-7.78 (4H, m), 7.50-7.10 (6H, m), 4.04-3.75 (3H, br), 2.27-2.02 and 1.96-1.74 (each 1 H, m), 0.90 (3H, br);

TLC : R_f 0.37 (acetic acid:methanol:chloroform=1:3:30).

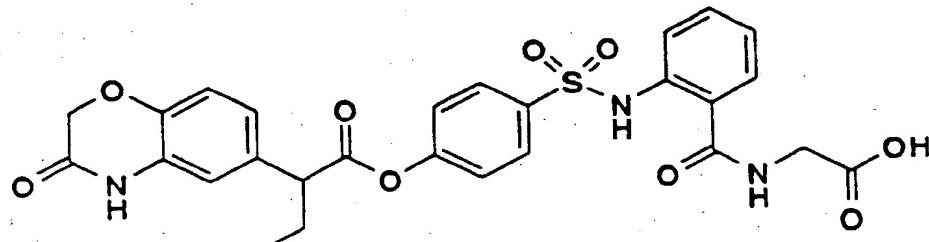
20

Example 2(126)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(2H-1,4-benzoxazin-3-on-6yl)butanoic acid es-
ter

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35

NMR (DMSO-d₆): δ 10.69 (1H, s), 9.53 (1H, t-like), 8.29 (1H, s), 7.83-7.73 (3H, m), 7.49-7.39 (2H, m), 7.20-6.91 (6H, m), 4.55 (2H, s), 3.90-3.86 (2H, d-like), 3.73 (1H, t, J=7Hz), 2.14-1.98 and 1.80-1.66 (each 1H, m), 0.88 (3H, t, J=7Hz);

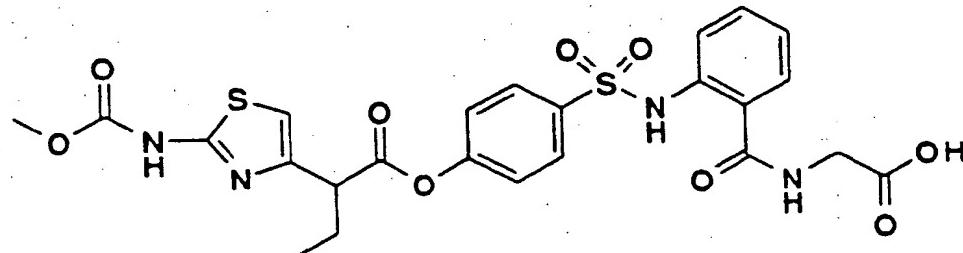
TLC : R_f 0.38 (acetic acid:methanol:chloroform=1:3:30).

Example 2(127)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(2-(N-methoxycarbonylamino)thiazol-4-yl)bu-
tanoic acid ester

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NMR (DMSO-d₆): δ 12.30 (1H, br), 11.81 (2H, br), 9.24 (1H, t-like), 7.81 (2H, d, J=7Hz), 7.74 (1H, d, J=8Hz), 7.51-7.45 (2H, m), 7.25-7.10 (3H, m), 7.07 (1H, s), 3.90 (1H, t, J=7Hz), 3.89 (2H, d, J=4Hz), 3.73 (3H, s), 2.12-1.81 (2H, m), 0.90 (3H, t, J=7Hz);

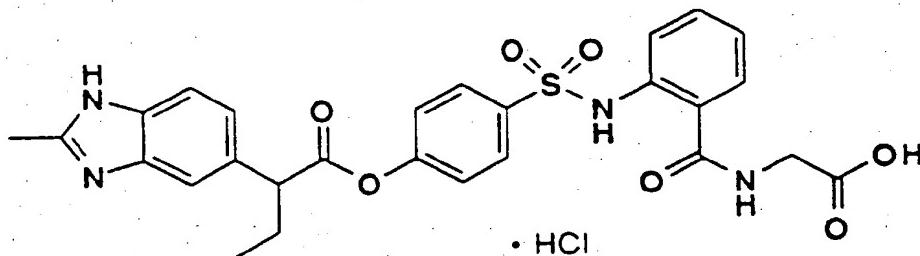
TLC : Rf 0.28 (chloroform:methanol:water=8:2:0.2).

5

Example 2(128)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(2-methylbenzimidazol-5-yl)butanoic acid ester
hydrochloride

10



15

NMR (CD₃OD): δ 7.75-7.68 (4H, m), 7.63-7.57 (3H, m), 7.46-7.37 (1H, m), 7.16-7.07 (3H, m), 4.00 (1H, t, J=8Hz),
3.94 (2H, s), 2.85 (3H, s), 2.34-2.15 and 2.06-1.88 (each 1H, m), 0.97 (3H, t, J=7Hz);

20

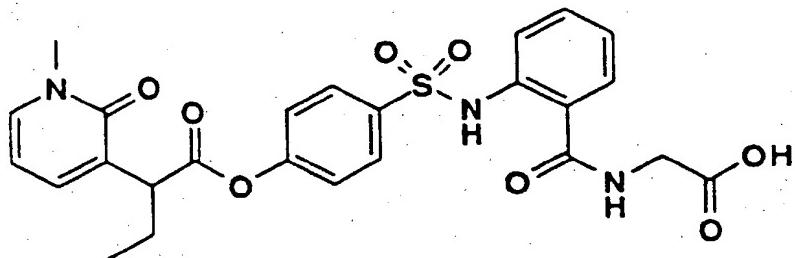
TLC : Rf 0.26 (chloroform:methanol:water=8:2:0.2).

25

Example 2(129)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(1H-1-methyl-2-pyridon-3-yl)butanoic acid es-
ter

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NMR (DMSO-d₆): δ 12.59 (1H, br), 11.65 (1H, br), 9.23 (1H, t-like), 7.82-7.63 (4H, m), 7.49-7.40 (3H, m), 7.25-7.09 (3H, m), 6.23 (1H, t, J=7Hz), 3.90 (2H, d, J=6Hz), 3.72 (1H, t, J=7Hz), 3.45 (3H, s), 2.04-1.70 (2H, m), 0.88 (3H, t, J=7Hz);

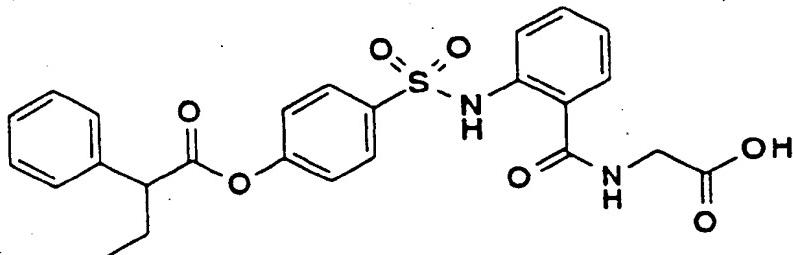
TLC : Rf 0.27 (chloroform:methanol:water=8:2:0.2).

50

Example 2(130)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester

55



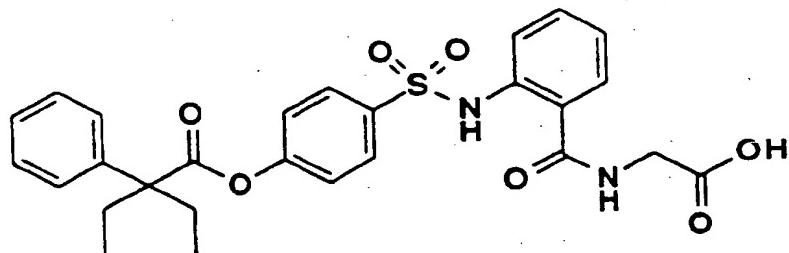
NMR (CDCl_3): δ 7.67 (3H, m), 7.50-7.20 (7H, m), 7.08 (1H, t, $J=8\text{Hz}$), 6.97 (2H, d, $J=8\text{Hz}$), 6.60 (1H, s), 5.69 (2H, brs), 4.00 (2H, m), 3.66 (1H, t, $J=7\text{Hz}$), 2.16 (1H, m), 1.86 (1H, m), 0.94 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.23 (chloroform:methanol=5:1).

15

Example 2(131)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-phenyl-2-ethylbutanoic acid ester

20



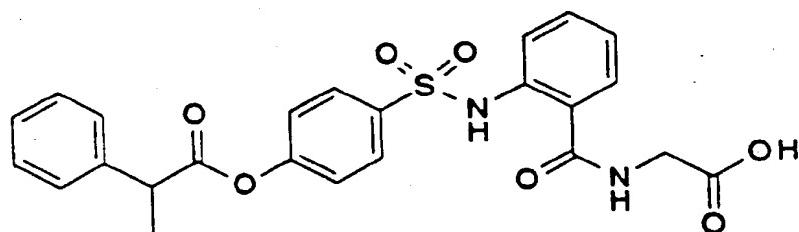
NMR (DMSO-d_6): δ 12.63 (1H, br), 11.67 (1H, br), 9.22 (1H, t-like), 7.82-7.70 (3H, m), 7.51-7.07 (10H, m), 3.89 (2H, d, $J=6\text{Hz}$), 2.09 (4H, m), 0.76 (6H, m);
TLC : Rf 0.58 (acetic acid:methanol:chloroform=1:3:30).

35

Example 2(132)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-phenylpropanoic acid ester

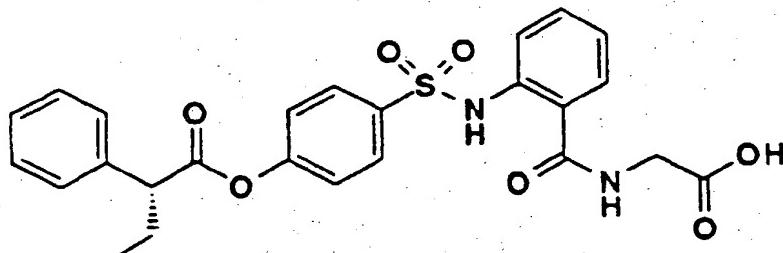
40



NMR ($\text{d}_6\text{-DMSO}$): δ 12.73 (1H, br), 11.59 (1H, br), 9.25-9.19 (1H, t-like), 7.82-7.70 (3H, m), 7.50-7.10 (10H, m), 4.10 (1H, q, $J=7\text{Hz}$), 3.89 (2H, d, $J=5\text{Hz}$), 1.49 (3H, d, $J=7\text{Hz}$);
TLC : Rf 0.32 (acetic acid:methanol:chloroform=1:2:40).

55 Example 2(133)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2R-phenylbutanoic acid ester

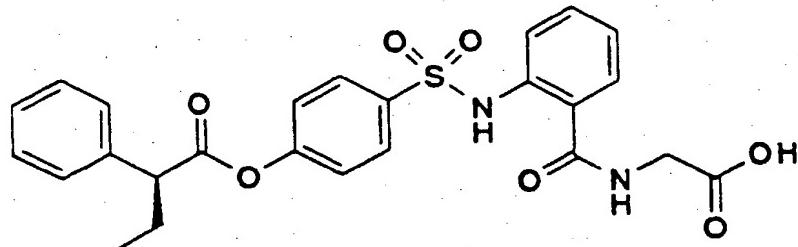


NMR (CDCl_3): δ 10.22 (1H, s), 7.71-7.65 (3H, m), 7.49-7.26 (6H, m), 7.15-7.10 (2H, m), 6.99-6.95 (2H, m), 6.49 (1H, br), 6.36 (1H, br), 4.01 (2H, d, $J=5\text{Hz}$), 3.65 (1H, t, $J=7\text{Hz}$), 2.24-2.11 and 1.95-1.81 (each 1H, m), 0.95 (3H, t, $J=7\text{Hz}$);

15 TLC : Rf 0.36 (acetic acid:methanol:chloroform=1:2:40).

Example 2(134)

20 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2S-phenylbutanoic acid ester

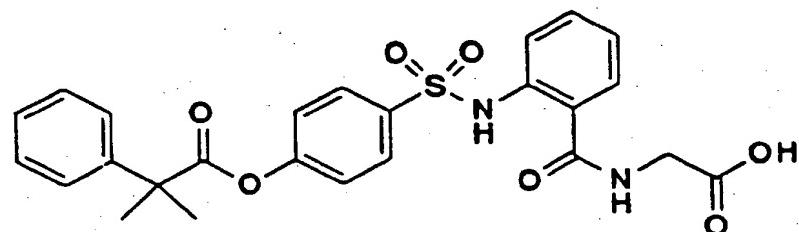


NMR (CDCl_3): δ 10.29 (1H, s), 7.70-7.65 (3H, m), 7.45-7.26 (6H, m), 7.13-7.05 (2H, m), 7.00-6.96 (2H, m), 6.60 (1H, br), 4.01 (2H, d, $J=5\text{Hz}$), 3.66 (1H, t, $J=8\text{Hz}$), 2.24-2.10 and 1.95-1.81 (each 1H, m), 0.95 (3H, t, $J=7\text{Hz}$);

35 TLC : Rf 0.36 (acetic acid:methanol:chloroform=1:2:40).

Example 2(135)

40 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-phenyl-2-methylpropanoic acid ester



NMR (DMSO-d_6): δ 12.67 (1H, br), 11.65 (1H, br), 9.22 (1H, t-like), 7.82-7.71 (3H, m), 7.52-7.09 (10H, m), 3.89 (2H, d, $J=6\text{Hz}$), 1.63 (6H, s);

55 TLC : Rf 0.34 (acetic acid:methanol:chloroform=1:3:30).

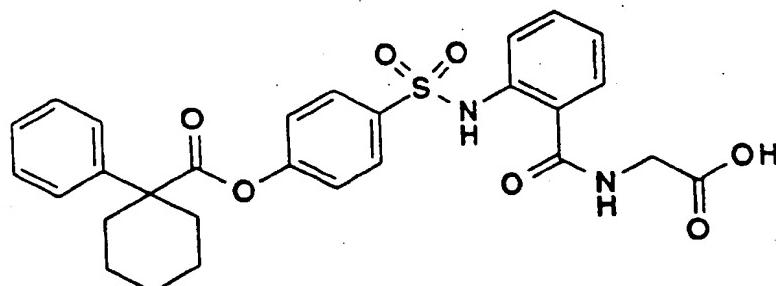
Example 2(136)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-phenylcyclohexanecarboxylic acid ester

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NMR (DMSO-d₆): δ 12.72 (1H, br), 11.61 (1H, br), 9.24 (1H, t-like), 7.81-7.70 (3H, m), 7.48-7.25 (7H, m), 7.14-7.10

(3H, m), 3.88 (2H, d, J=6Hz), 2.56-2.41 (2H, m), 1.85-1.23 (8H, m);

TLC : Rf 0.48 (acetic acid:methanol:chloroform=1:3:30).

20

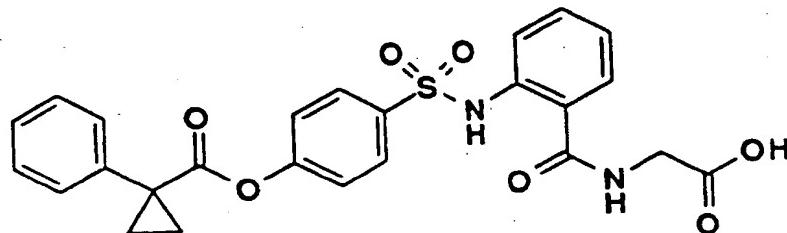
Example 2(137)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-phenylcyclopropanecarboxylic acid ester

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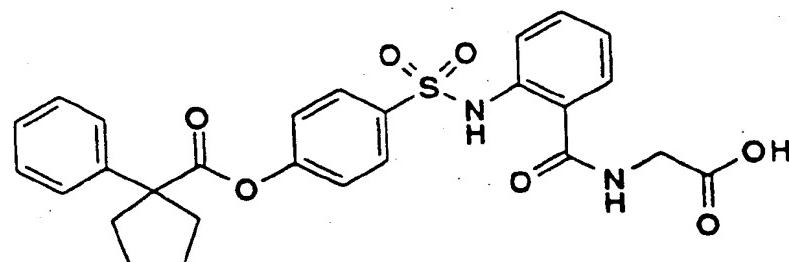
Example 2(138)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-phenylcyclopentanecarboxylic acid ester

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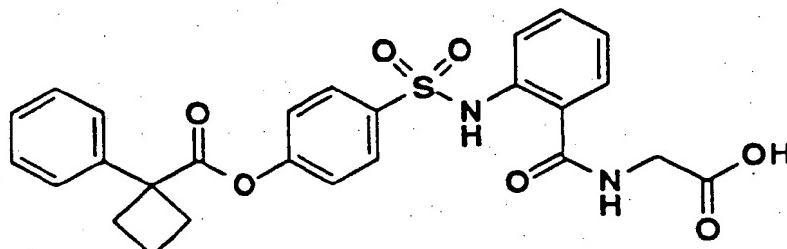


NMR (DMSO-d₆): δ 9.3-9.1 (1H, br), 7.8-7.7 (3H, m), 7.5-7.2 (7H, m), 7.2-7.0 (3H, m), 3.87 (2H, d, J=5Hz), 2.7-2.5 (2H, m), 2.1-1.9 (2H, m), 1.9-1.6 (4H, m);

TLC : Rf 0.21 (acetic acid:methanol:chloroform=1:2:40).

Example 2(139)

5 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-phenylcyclobutanecarboxylic acid ester

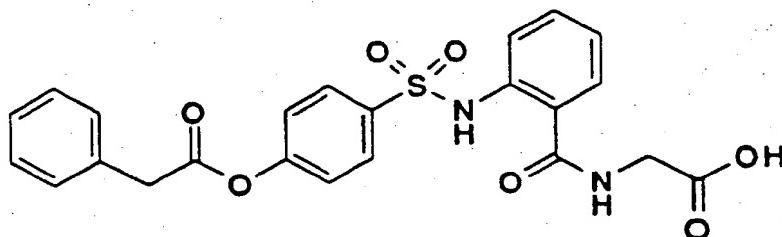


NMR (DMSO-d₆): δ 9.3-9.1 (1H, brt), 7.8-7.6 (3H, m), 7.5-7.2 (7H, m), 7.2-7.1 (3H, m), 3.88 (2H, d, J=5Hz),
3.0-2.8 (2H, m), 2.6-2.4 (2H, m), 2.1-1.8 (2H, m);

20 TLC : Rf 0.19 (acetic acid:methanol:chloroform=1:2:40).

Example 2(140)

25 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-phenylacetic acid ester

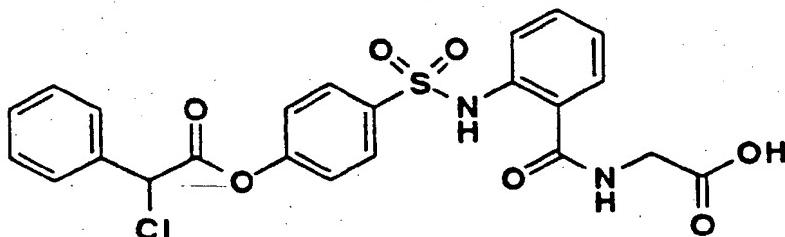


NMR (DMSO-d₆): δ 10.01-9.76 (1H, br), 7.82-7.76 (4H, m), 7.41-7.22 (9H, m), 7.03-6.90 (1H, m), 3.96 (2H, s),
3.86 (2H, m);

40 TLC : Rf 0.66 (acetic acid:methanol:chloroform=1:3:30).

Example 2(141)

45 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-chloro-2-phenylacetic acid ester

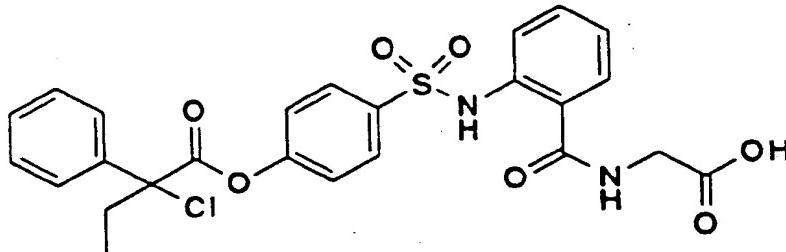


NMR(DMSO-d₆): δ 9.2-9.1 (1H, brt), 7.82 (2H, d, J=8Hz), 7.71 (1H, d, J=8Hz), 7.6-7.4 (7H, m), 7.29 (2H, d,
J=8Hz), 7.2-7.1 (1H, m), 6.26 (1H, s), 3.88 (2H, d, J=5Hz);

TLC : Rf 0.18 (acetic acid:methanol:chloroform=1:2:40).

Example 2(142)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-chloro-2-phenylbutanoic acid ester

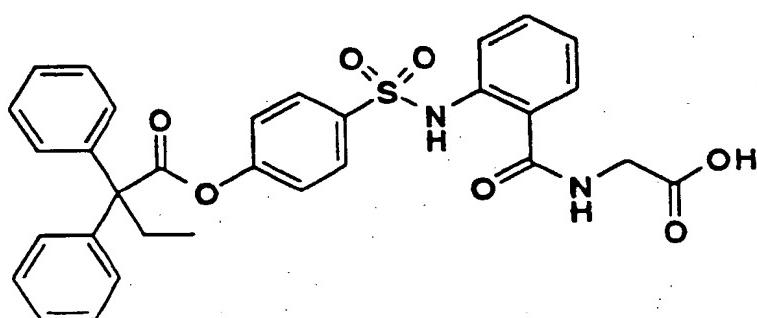


15 NMR (DMSO-d₆): δ 9.3-9.2 (1H, br), 7.93 (2H, d, J=8Hz), 7.72 (1H, d, J=8Hz), 7.65-7.55 (2H, m), 7.6-7.4 (5H, m), 7.37 (2H, d, J=8Hz), 7.2-7.1 (1H, m), 3.88 (2H, d, J=5Hz), 2.6-2.4 (2H, m), 0.97 (3H, t, J=7Hz);
TLC : R_f 0.20 (acetic acid:methanol:chloroform=1:2:40).

20 Example 2(143)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2,2-diphenylbutanoic acid ester

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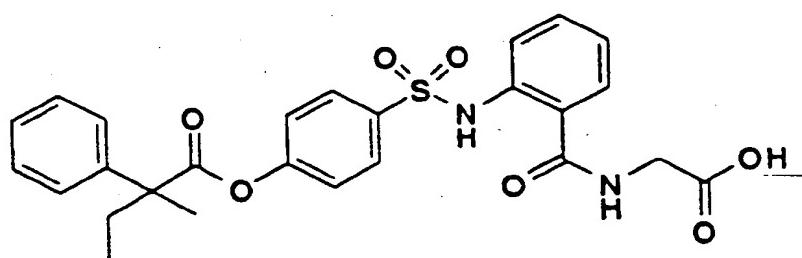


40 NMR (DMSO-d₆): δ 9.51-9.38 (1H, m), 7.86-7.68 (4H, m), 7.51-7.20 (11 H, m), 7.19-7.01 (4H, m), 3.84 (2H, d, J=6Hz), 2.53-2.41 (2H, m), 0.79 (3H, t, J=7Hz);
TLC : R_f 0.44 (acetic acid:methanol:chloroform=1:3:30).

Example 2(144)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-methyl-2-phenylbutanoic acid ester

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NMR (DMSO-d₆): δ 9.3-9.2 (1H, br), 7.88 (2H, d, J=8Hz), 7.70 (1H, d, J=8Hz), 7.5-7.1 (10H, m), 3.88 (2H, d,

$J=5\text{Hz}$), 2.2-1.9 (2H, m), 1.57 (3H, s), 0.85 (3H, t, $J=7\text{Hz}$);
 TLC : Rf 0.15 (acetic acid:methanol:chloroform=1:2:40).

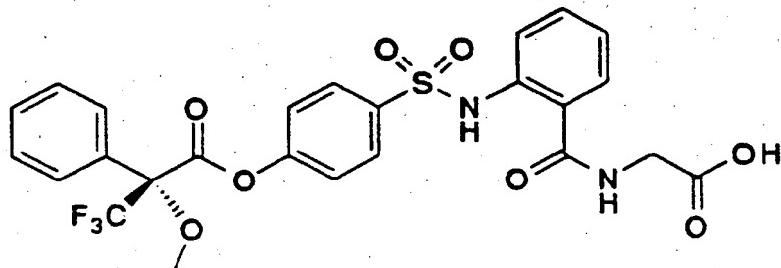
Example 2(145)

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4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2R-trifluoromethyl-2-phenyl-2-methoxyacetic acid ester

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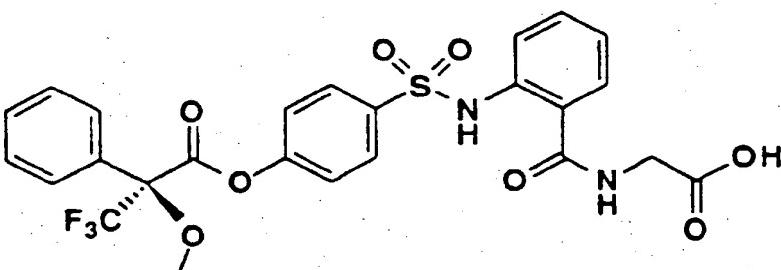
NMR (CD_3OD): δ 7.81 (2H, d, $J=8.8\text{Hz}$), 7.62 (4H, m), 7.48 (4H, m), 7.27 (2H, d, $J=8.8\text{Hz}$), 7.15 (1H, t, $J=7.6\text{Hz}$), 3.97 (2H, s), 3.65 (3H, s);
 TLC : Rf 0.28 (chloroform:methanol:water=9:1:0.1).

25 Example 2(146)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2S-trifluoromethyl-2-phenyl-2-methoxyacetic acid ester

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NMR (CD_3OD): δ 7.81 (2H, d, $J=8.6\text{Hz}$), 7.62 (4H, m), 7.47 (4H, m), 7.27 (2H, d, $J=8.6\text{Hz}$), 7.15 (1H, t, $J=7.6\text{Hz}$), 3.97 (2H, s), 3.65 (3H, s);
 TLC : Rf 0.27 (chloroform:methanol:water=9:1:0.1).

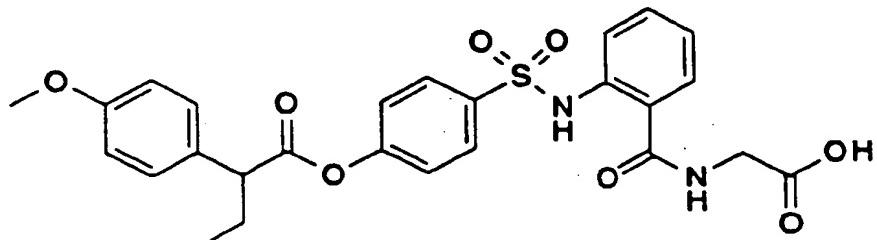
45

Example 2(147)

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4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-methoxyphenyl)butanoic acid ester

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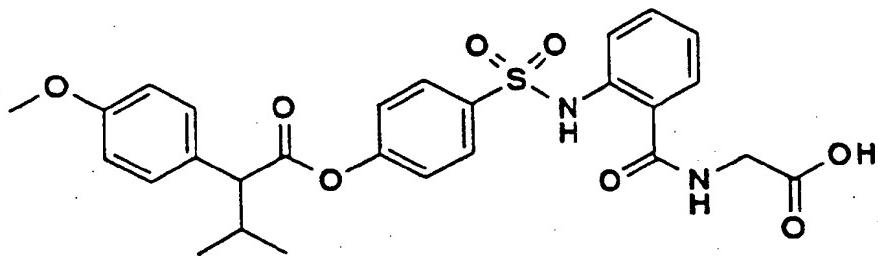


NMR(CDCl_3): δ 7.70-7.64 (2H, m), 7.42 (2H, t, $J=8\text{Hz}$), 7.27-7.06 (4H, m), 6.97 (2H, d, $J=9\text{Hz}$), 6.88 (2H, d, $J=9\text{Hz}$), 6.55 (1H, t-like), 4.82 (2H, brs), 3.99 (2H, d, $J=5\text{Hz}$), 3.79 (3H, s), 3.61 (1H, t, $J=8\text{Hz}$), 2.12 and 1.85(each 1H, m), 0.94 (3H, t, $J=7\text{Hz}$);

15 TLC : Rf 0.50 (acetic acid:methanol:chloroform=1:3:30).

Example 2(148)

20 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-methoxyphenyl)-3-methylbutanoic acid es-
ter

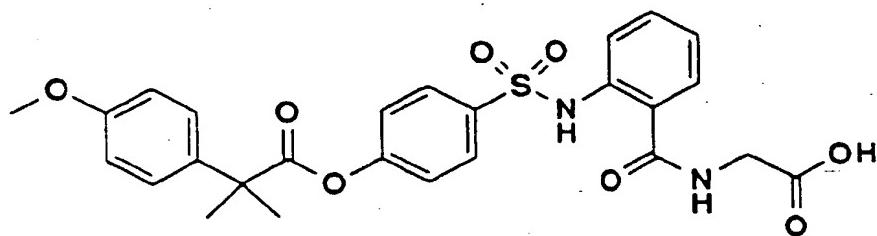


35 NMR (CDCl_3): δ 10.20 (1H, s), 7.73-7.64 (3H, m), 7.48-7.39 (2H, m), 7.33-7.22 (2H, m), 7.12 (1H, t, $J=8\text{Hz}$),
6.98-6.85 (4H, m), 6.46 (1H, t-like), 5.08 (1H, br), 4.00 (2H, d, $J=4\text{Hz}$), 3.80 (3H, s), 3.31 (1H, d, $J=10\text{Hz}$), 2.46-2.27
(1H, m), 1.12 and 0.76 (each 3H, each d, $J=7\text{Hz}$);

TLC : Rf 0.58 (acetic acid:methanol:chloroform=1:3:30).

Example 2(149)

40 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(4-methoxyphenyl)-2-methylpropanoic acid ester



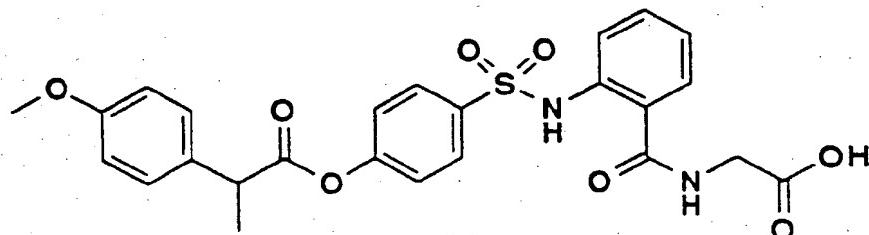
55 NMR (DMSO-d_6): δ 12.66 (1H, br), 11.64 (1H, br), 9.23 (1H, t-like), 7.81-7.70 (3H, m), 7.52-7.10 (7H, m), 6.92
(2H, d, $J=9\text{Hz}$), 3.89 (2H, d, $J=6\text{Hz}$), 3.74 (3H, s), 1.60 (6H, s);
TLC : Rf 0.35 (acetic acid:methanol:chloroform=1:3:30).

Example 2(150)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-methoxyphenyl)propanoic acid ester

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NMR (DMSO-d₆): δ 12.67 (1H, br), 11.64 (1H, br), 9.21 (1H, t-like), 7.81-7.70 (3H, m), 7.52-7.41 (2H, m), 7.30-7.09 (5H, m), 6.91 (2H, d, J=8Hz), 4.00 (1H, q, J=7Hz), 3.88 (2H, d, J=5Hz), 3.73 (3H, s), 1.46 (3H, d, J=7Hz);
TLC : R_f 0.30 (acetic acid:methanol:chloroform=1:3:30).

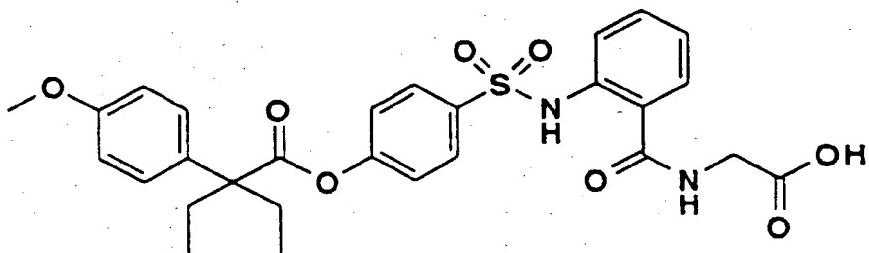
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Example 2(151)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(4-methoxyphenyl)-2-ethylbutanoic acid ester

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NMR (DMSO-d₆): δ 12.68 (1H, br), 11.62 (1H, br), 9.24 (1H, t-like), 7.82-7.71 (3H, m), 7.52-7.46 (2H, m), 7.30-7.09 (5H, m), 6.93 (2H, d, J=9Hz), 3.89 (2H, d, J=6Hz), 3.75 (3H, s), 2.10-1.98 (4H, m), 0.75 (6H, t, J=7Hz);
TLC : R_f 0.34 (acetic acid:methanol:chloroform=1:3:30).

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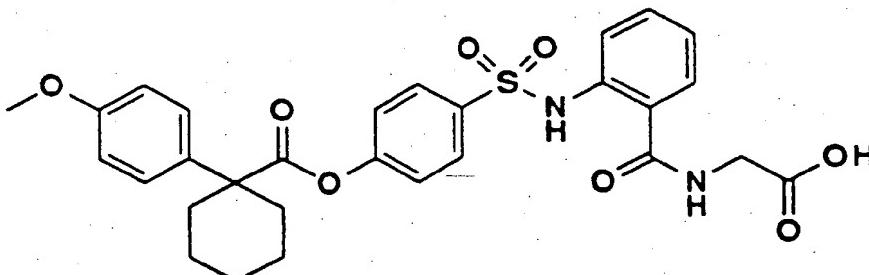
Example 2(152)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-methoxyphenyl)cyclohexanecarboxylic acid es-
ter

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NMR (DMSO-d₆): δ 12.71 (1H, br), 11.57 (1H, br), 9.19 (1H, t-like), 7.77-7.66 (3H, m), 7.44-7.30 (4H, m), 7.13-7.04

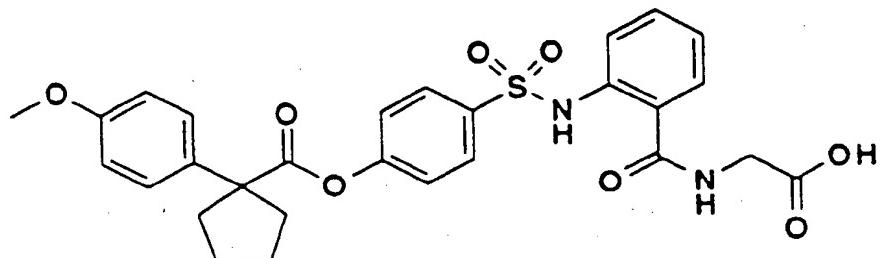
(3H, m), 6.89 (2H, d, J=8Hz), 3.85 (2H, d, J=6Hz), 3.69 (3H, s), 2.47-2.36 (2H, m), 1.77-1.20 (8H, m);
 TLC : Rf 0.51 (acetic acid:methanol:chloroform=1:3:30).

Example 2(153)

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4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-methoxyphenyl)cyclopentanecarboxylic acid ester

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NMR (DMSO-d₆): δ 12.69 (1H, br), 11.66 (1H, br), 9.23 (1H, t-like), 7.80-7.71 (3H, m), 7.51-7.29 (4H, m), 7.18-7.07 (3H, m), 6.92 (2H, dd, J=1 and 8Hz), 3.89 (2H, d, J=5Hz), 3.74 (3H, s), 2.66-2.53 (2H, m), 2.01-1.87 (2H, m), 1.79-1.67 (4H, m);

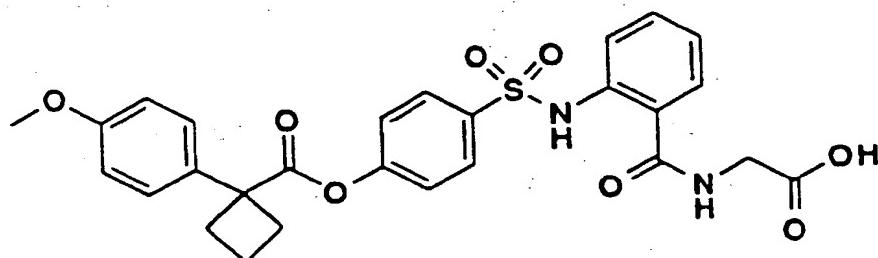
TLC : Rf 0.68 (acetic acid:methanol:chloroform=1:3:30).

25 Example 2(154)

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4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-methoxyphenyl)cyclobutanecarboxylic acid ester

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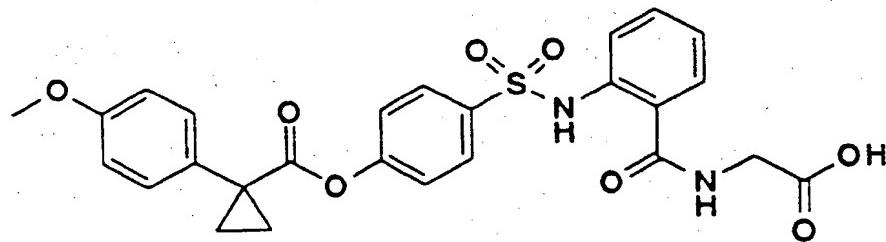
NMR (DMSO-d₆): δ 9.2-9.1 (1H, brt), 7.8-7.7 (3H, m), 7.5-7.4 (2H, m), 7.30 (2H, d, J=8Hz), 7.2-7.0 (3H, m), 6.92 (2H, d, J=8Hz), 3.87 (2H, d, J=5Hz), 3.74 (3H, s), 2.9-2.7 (2H, m), 2.6-2.4 (2H, br), 2.1-1.7 (2H, br);
 TLC : Rf 0.21 (acetic acid:methanol:chloroform=1:2:40).

45 Example 2(155)

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4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-methoxyphenyl)cyclopropanecarboxylic acid ester

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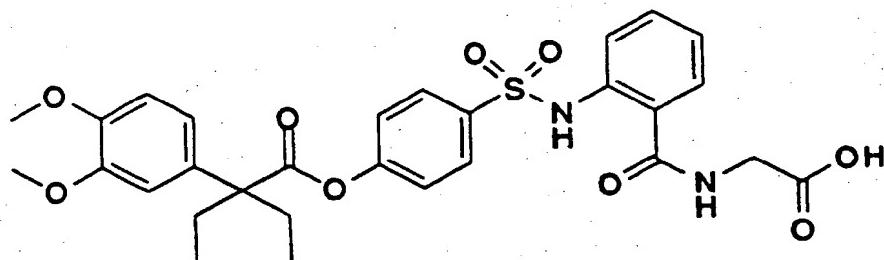
NMR (DMSO-d₆): δ 9.53-9.38 (1H, m), 7.79-7.72 (3H, m), 7.51-7.28 (4H, m), 7.26-7.19 (2H, m), 7.16-7.00 (1H, m), 6.89-6.84 (2H, m), 3.88 (2H, d, J=6Hz), 3.73 (3H, s), 1.70-1.61 (2H, m), 1.38-1.29 (2H, m);
TLC : Rf 0.49 (acetic acid:methanol:chloroform=1:3:30).

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Example 2(156)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(3,4-dimethoxyphenyl)-2-ethylbutanoic acid ester

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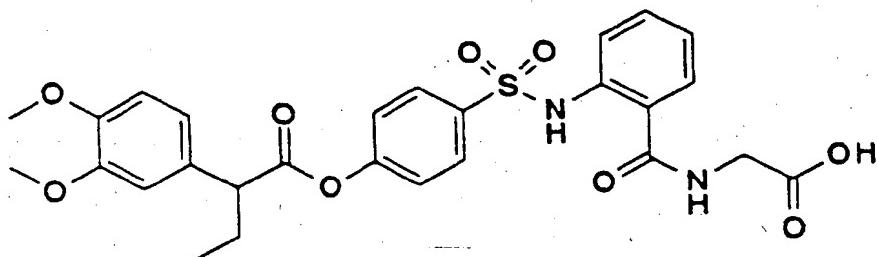
NMR (DMSO-d₆): δ 9.52-9.38 (1H, br), 7.83-7.71 (3H, m), 7.53-7.39 (2H, m), 7.19-7.02 (3H, m), 7.00-6.78 (3H, m), 3.89 (2H, d, J=6Hz), 3.76 (6H, s), 2.06 (4H, q, J=7Hz), 0.78 (6H, t, J=7Hz);
TLC : Rf 0.39 (acetic acid:methanol:chloroform=1:3:30).

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Example 2(157)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(3,4-dimethoxyphenyl)butanoic acid ester

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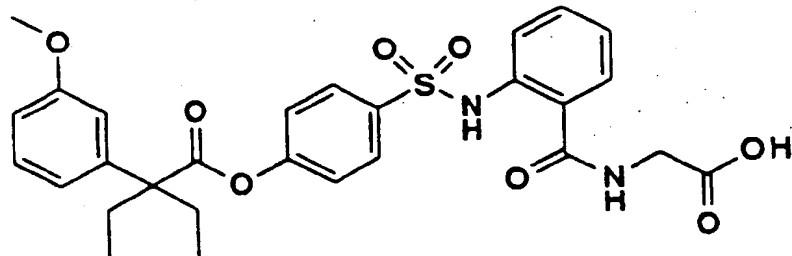


NMR (CDCl₃+CD₃OD): δ 7.45-7.41 (2H, m), 7.30-7.19 (2H, m), 7.18-7.01 (1H, m), 6.82-6.69 (3H, m), 6.56-6.52 (3H, m), 3.63 (2H, s), 3.53 (6H, s), 3.28 (1H, t, J=7Hz), 1.98-1.42 (2H, m), 0.63 (3H, t, J=7Hz);
TLC : Rf 0.64 (acetic acid:methanol:chloroform=1:3:30).

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Example 2(158)

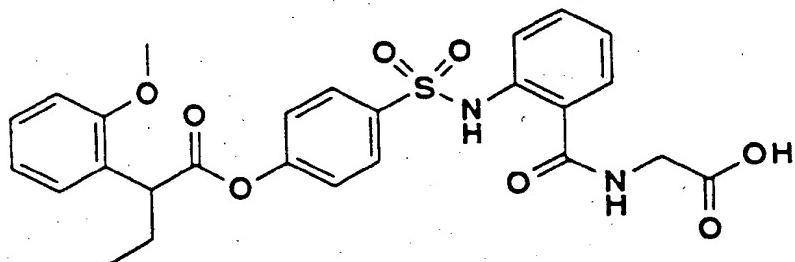
4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(3-methoxyphenyl)-2-ethylbutanoic acid ester



15 NMR (DMSO-d₆): δ 12.71 (1H, br), 11.65 (1H, br), 9.23 (1H, t-like), 7.83-7.71 (3H, m), 7.53-7.42 (2H, m), 7.35-7.10 (4H, m), 6.92-6.84 (3H, m), 3.89 (2H, d, J=6Hz), 3.75 (3H, s), 2.12-2.01 (4H, m), 0.76 (6H, t, J=7Hz);
TLC : Rf 0.39 (acetic acid:methanol:chloroform=1:2:40).

Example 2(159)

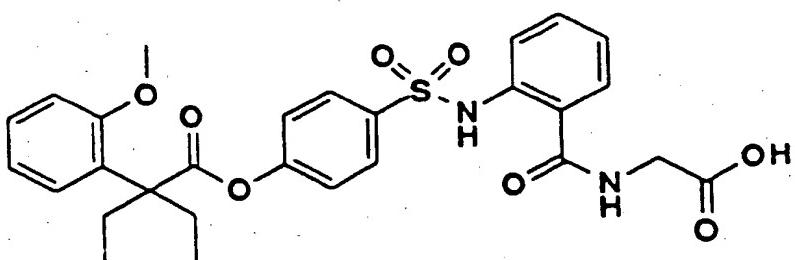
20 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(2-methoxyphenyl)butanoic acid ester



35 NMR (DMSO-d₆): δ 11.58 (1H, s), 9.24-9.18 (1H, m), 7.86-7.64 (3H, m), 7.57-7.44 (2H, m), 7.38-7.09 (5H, m), 7.08-6.91 (3H, m), 4.02-3.98 (1H, m), 3.88 (2H, d, J=6Hz), 3.77 (3H, s), 2.18-1.84 (2H, m), 0.87 (3H, t, J=7Hz);
TLC : Rf 0.41 (acetic acid:methanol:chloroform=1:3:30).

Example 2(160)

40 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(2-methoxyphenyl)-2-ethylbutanoic acid ester

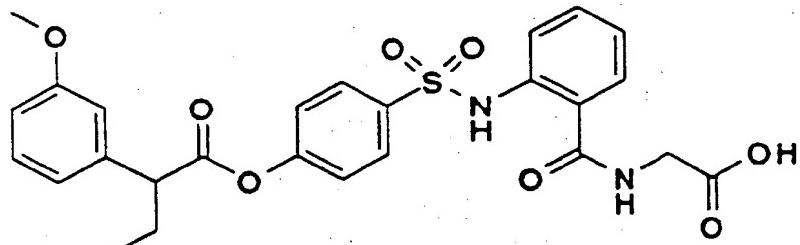


55 NMR (DMSO-d₆): δ 9.28-9.19 (1H, m), 7.82-7.69 (3H, m), 7.48-7.41 (2H, m), 7.28-7.08 (4H, m), 7.00-6.75 (4H, m), 3.89 (2H, d, J=6Hz), 3.77 (3H, s), 2.18-1.82 (4H, m), 0.86 (6H, t, J=7Hz);
TLC : Rf 0.39 (acetic acid:methanol:chloroform=1:3:30).

Example 2(161)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(3-methoxyphenyl)butanoic acid ester

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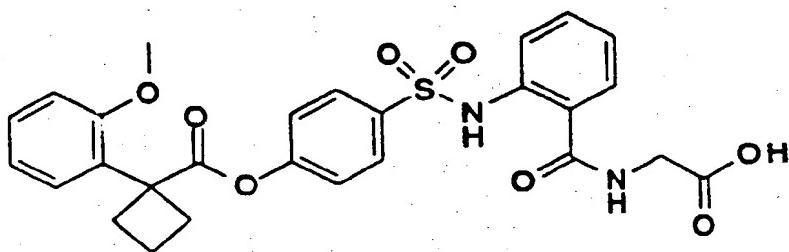
NMR (DMSO-d₆): δ 10.79 (1H, br), 7.85-7.79 (3H, m), 7.33-7.25 (2H, m), 7.17-7.06 (3H, m), 6.95-6.85 (3H, m), 6.74 (1H, t, J=7Hz), 3.85 (2H, d-like), 3.80-3.69 (1H, m), 3.75 (3H, s), 2.15-2.01 and 1.91-1.71 (each 1H, m), 0.89 (3H, t, J=7Hz);

TLC : Rf 0.47 (acetic acid:methanol:chloroform=1:2:40).

Example 2(162)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(2-methoxyphenyl)cyclobutanecarboxylic acid es-
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NMR (DMSO-d₆): δ 12.9-12.5 (1H, br), 11.7-11.4 (1H, br), 9.20 (1H, t-like), 7.78 (2H, d, J=8.6Hz), 7.72 (1H, d, J=7.4Hz), 7.52-7.38 (3H, m), 7.28 (1H, t-like), 7.20-7.08 (3H, m), 7.00 (2H, d, J=7.8Hz), 3.89 (2H, d, J=5.6Hz), 3.77 (3H, s), 2.85-2.65 (2H, m), 2.55-2.35 (2H, m) 2.20-2.00 and 2.00-1.80(each 1H, m);

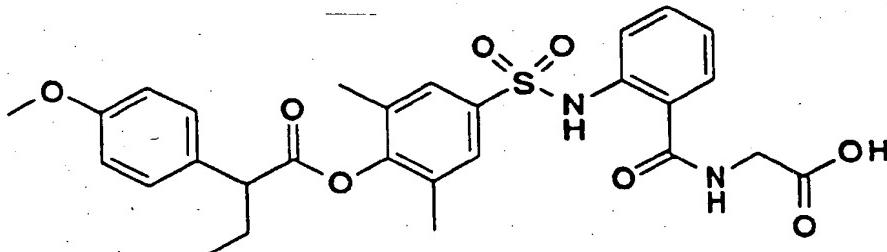
TLC : Rf 0.30 (acetic acid:methanol:chloroform=1:2:40).

Example 2(163)

45 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2,6-dimethylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester

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EP 0 769 498 A1

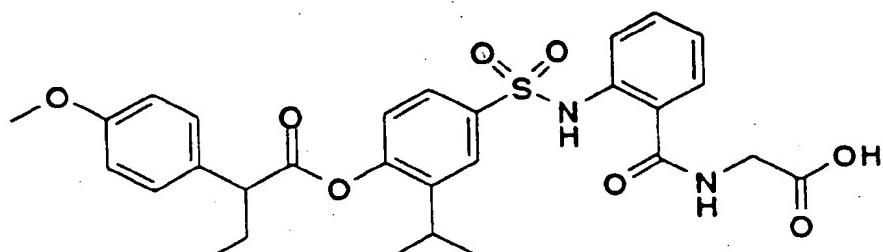
NMR (DMSO-d₆): δ 9.8-9.5 (brs, 1H), 7.8-7.7 (m, 1H), 7.5-7.2 (m, 6H), 7.1-6.8 (m, 4H), 4.0-3.7 (m, 3H), 3.74 (s, 3H), 2.2-1.7 (m, 8H), 0.90 (t, J=7.0Hz, 3H);
 TLC : Rf 0.30 (hexane:ethyl acetate=1:1).

5 Example 2(164)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2-isopropylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester

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NMR (CDCl₃): δ 10.0-9.9 (m, 1H), 7.8-7.7 (m, 1H), 7.6-7.2 (m, 6H), 7.2-7.0 (m, 1H), 7.0-6.8 (m, 3H), 6.5-6.3 (m, 1H), 4.0-3.4 (m, 2H), 3.80 (s, 3H), 3.64 (t, J=7.8Hz, 1H), 2.7-2.5 (m, 1H), 2.3-2.1 (m, 1H), 2.0-1.8 (m, 1H), 0.95 (t, J=7.6Hz, 3H), 0.83 (dd, J=2.0, 6.9Hz, 6H);

TLC : Rf 0.49 (chloroform:methanol=3:1).

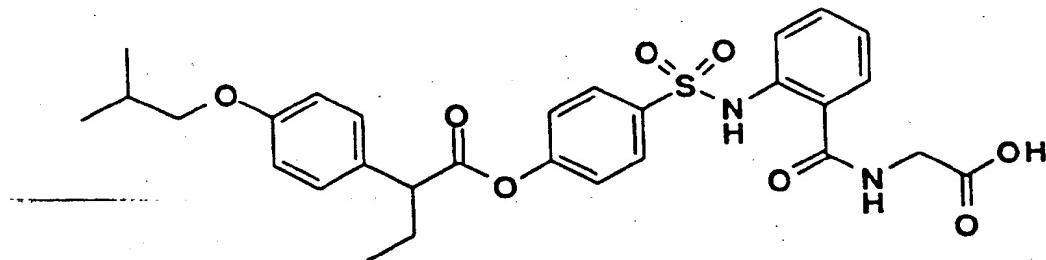
Example 2(165)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(2-methylpropyloxy)phenyl)butanoic acid ester

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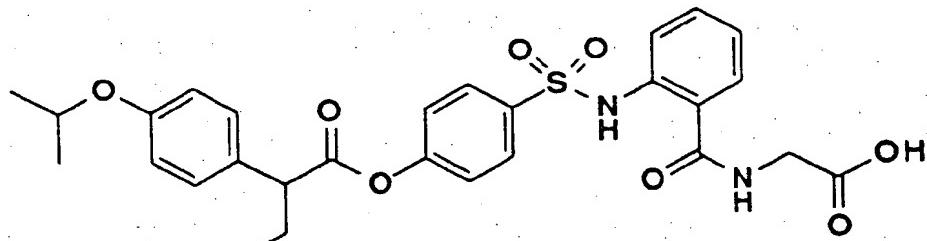


NMR (DMSO-d₆): δ 9.25-9.07 (1H, br), 8.02-7.98 (1H, d-like), 7.89-7.80 (2H, d-like), 7.79-7.65 (2H, m), 7.59-7.38 (3H, m), 7.18-7.09 (1H, m), 7.01-6.77 (2H, m), 3.97-3.65 (3H, m), 3.80 (3H, s), 3.97-3.65 (3H, s), 1.19 (6H, d, J=7Hz);
 TLC : Rf 0.37 (acetic acid:methanol:chloroform=1:3:30).

Example 2(166)

50 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-isopropyloxyphenyl)butanoic acid ester

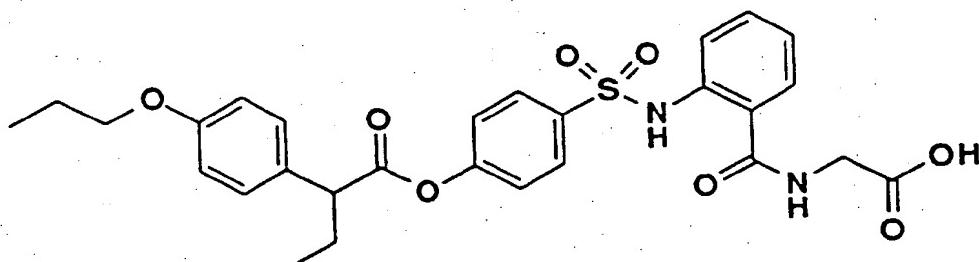
55



15 NMR (DMSO-d₆): δ 11.58 (1H, s), 9.22-9.13 (1H, m), 7.80-7.63 (4H, m), 7.49-7.40 (2H, m), 7.25-7.06 (5H, m),
6.88-6.84 (2H, m), 4.63-4.48 (1H, m), 3.88 (2H, d, J=6Hz), 3.72 (1H, t, J=7Hz), 2.18-1.63 (2H, m), 1.26 (6H, d, J=6Hz),
0.88 (3H, t, J=7Hz);
TLC : R_f 0.34 (acetic acid:methanol:chloroform=1:3:30).

Example 2(167)

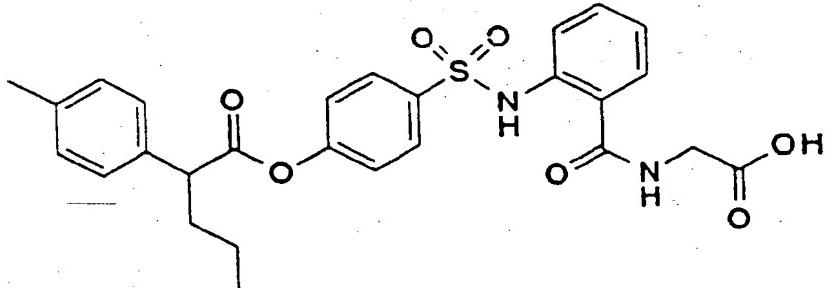
20 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-propyloxyphenyl)butanoic acid ester



35 NMR (DMSO-d₆): δ 9.38-9.20 (1H, m), 7.81-7.77 (2H, d-like), 7.77-7.70 (2H, m), 7.49-7.31 (2H, m), 7.28-7.03
(5H, m), 6.93-6.89 (2H, d-like), 3.94-3.87 (4H, m), 3.72 (1H, t, J=6Hz), 2.20-1.98 (1H, m), 1.83-1.62 (3H, m), 0.98 (3H,
t, J=7Hz), 0.88 (3H, t, J=7Hz);
TLC : R_f 0.35 (acetic acid:methanol:chloroform=1:3:30).

Example 2(168)

40 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-methylphenyl)pentanoic acid ester



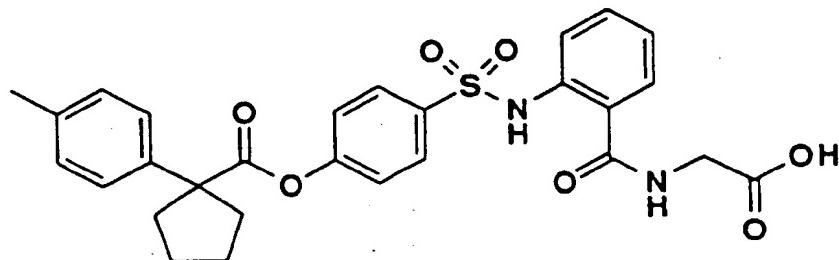
55 NMR (CDCl₃): δ 10.20 (1H, s), 7.68 (1H, d, J=8Hz), 7.65 (2H, d, J=8Hz), 7.50-7.35 (2H, m), 7.25-7.05 (5H, m),
6.95 (2H, d, J=8Hz), 6.6-6.5 (1H, br), 4.00 (2H, d, J=5Hz), 3.72 (1H, t, J=7Hz), 2.35 (3H, s), 2.2-2.0 (1H, m), 1.9-1.7
(1H, m), 1.4-1.2 (2H, m), 0.92 (3H, t, J=7Hz);
TLC : R_f 0.25 (chloroform:methanol:acetic acid=40:2:1).

Example 2(169)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-methylphenyl)cyclopentanecarboxylic acid ester

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NMR (DMSO-d₆): δ 12.70 (1H, br), 11.66 (1H, br), 9.23 (1H, t-like), 7.80-7.70 (3H, m), 7.51-7.41 (2H, m), 7.33-7.29 (2H, m), 7.19-7.09 (5H, m), 3.89 (2H, d, J=6Hz), 2.65-2.55 (2H, m), 2.29 (3H, s), 2.04-1.90 (2H, m), 1.79-1.65 (4H, m);
TLC : Rf 0.69 (acetic acid:methanol:chloroform=1:3:30).

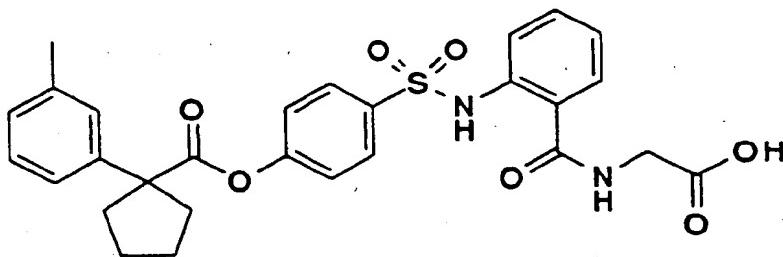
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Example 2(170)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(3-methylphenyl)cyclopentanecarboxylic acid ester

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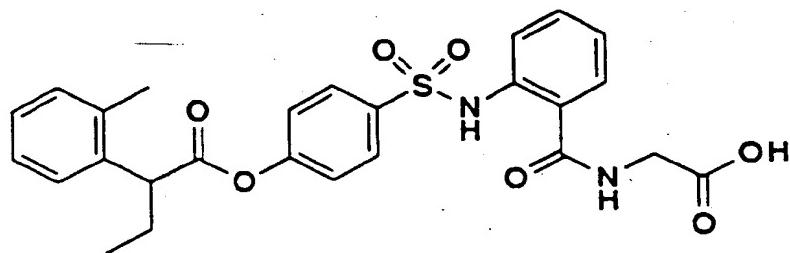
NMR (DMSO-d₆): δ 9.22-9.18 (1H, m), 7.80-7.68 (3H, m), 7.49-7.41 (2H, m), 7.29-7.10 (7H, m), 3.89 (2H, d, J=6Hz), 2.70-2.51 (2H, m), 2.32 (3H, s), 2.04-1.83 (2H, m), 1.74-1.60 (4H, m);
TLC : Rf 0.40 (acetic acid:methanol:chloroform=1:3:30).

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Example 2(171)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(2-methylphenyl)butanoic acid ester

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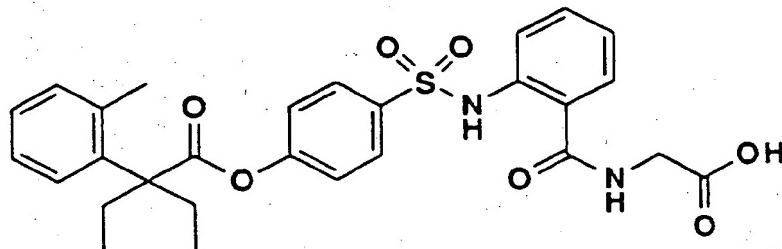
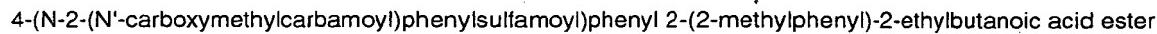
55

NMR (DMSO-d₆): δ 9.4-9.2 (1H, br), 7.8-7.7 (3H, m), 7.5-7.4 (2H, m), 7.3-7.0 (7H, m), 4.06 (1H, t, J=7Hz), 3.88

EP 0 769 498 A1

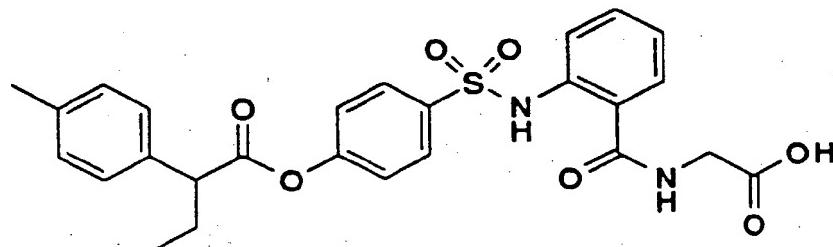
(2H, d, $J=5$ Hz), 2.37 (3H, s), 2.2-2.0 (1H, m), 1.9-1.7 (1H, m), 0.87 (3H, t, $J=7$ Hz);
 TLC : Rf 0.16 (acetic acid:methanol:chloroform=1:2:40).

Example 2(172)



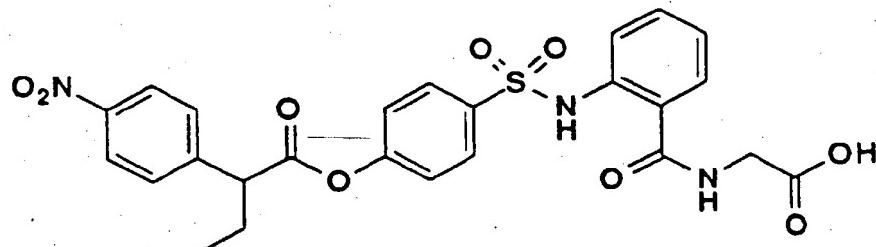
²⁰ NMR (DMSO-d₆): δ 9.5-9.3 (1H, br), 7.9-7.6 (3H, m), 7.6-7.0 (9H, br), 4.0-3.8 (2H, br), 2.27 (3H, s), 2.3-1.9 (4H, br), 0.8-0.6 (6H, br);
TLC: Rf 0.15 (acetic acid:methanol:chloroform=1:2:40)

Example 2(173)



40 NMR(DMSO-d₆): δ 10.61-10.32 (1H, m), 7.85-7.74 (3H, m), 7.36-7.04 (8H, m), 6.90-6.75 (1H, m), 3.92-3.83 (2H, m), 3.77 (1H, t, J=7.6Hz), 2.29 (3H, s), 2.21-1.96 and 1.89-1.63 (each 1H, m), 0.87 (3H, t, J=7.4Hz);
TLC : Rf 0.23 (chloroform:methanol:water=8:2:0.2).

Example 2(174)

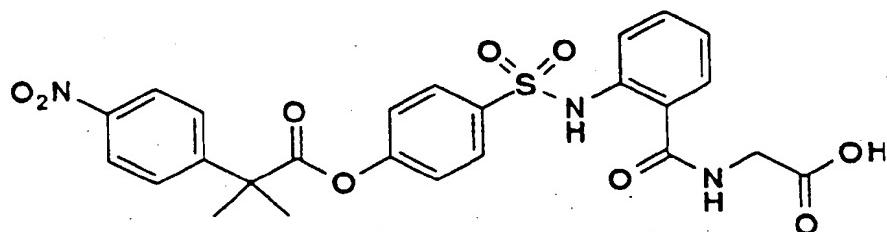


EP 0 769 498 A1

NMR ($\text{CDCl}_3 + \text{CD}_3\text{OD}$): δ 8.24 (2H, d, $J=8\text{Hz}$), 7.85-7.55 (6H, m), 7.10 (4H, m), 3.95 (2H, s), 3.87 (1H, t, $J=7\text{Hz}$), 2.25 and 1.98 (each 1H, m), 0.99 (3H, t, $J=7\text{Hz}$);
 TLC : Rf 0.33 (acetic acid:methanol:chloroform=1:3:30).

5 Example 2(175)

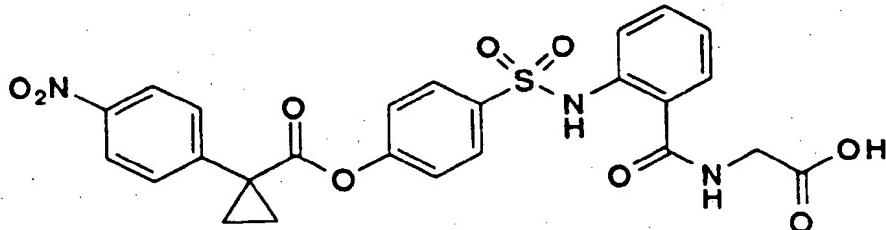
4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(4-nitrophenyl)-2-methylpropanoic acid ester



20 NMR (DMSO-d_6): δ 13.50-11.00 (2H, br), 9.30-9.16 (1H, m), 8.23 (2H, d, $J=8\text{Hz}$), 7.88-7.68 (5H, m), 7.55-7.40 (2H, m), 7.25 (2H, d, $J=8\text{Hz}$), 7.20-7.09 (1H, m), 3.89 (2H, d, $J=6\text{Hz}$), 1.68 (6H, s);
 TLC : Rf 0.41 (acetic acid:methanol:chloroform=1:3:30).

Example 2(176)

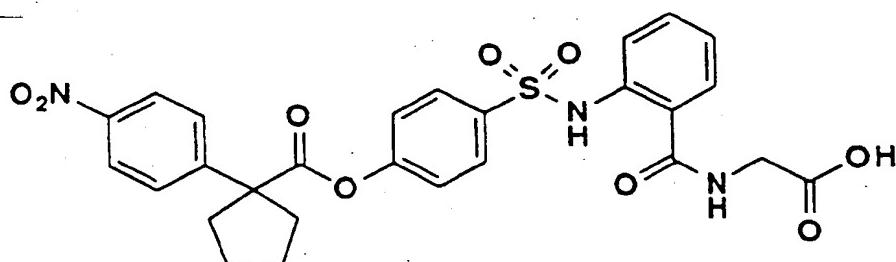
25 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclopropanecarboxylic acid ester



40 NMR (DMSO-d_6): δ 9.2-9.1 (1H, brt), 8.18 (2H, d, $J=8\text{Hz}$), 7.8-7.6 (5H, m), 7.5-7.4 (2H, m), 7.29 (2H, d, $J=8\text{Hz}$), 7.2-7.0 (1H, m), 3.90 (2H, d, $J=5\text{Hz}$), 1.77 (2H, dd, $J=6, 4\text{Hz}$), 1.48 (2H, dd, $J=6, 4\text{Hz}$);
 TLC : Rf 0.17 (acetic acid:methanol:chloroform=1:2:40).

Example 2(177)

45 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclopentanecarboxylic acid ester

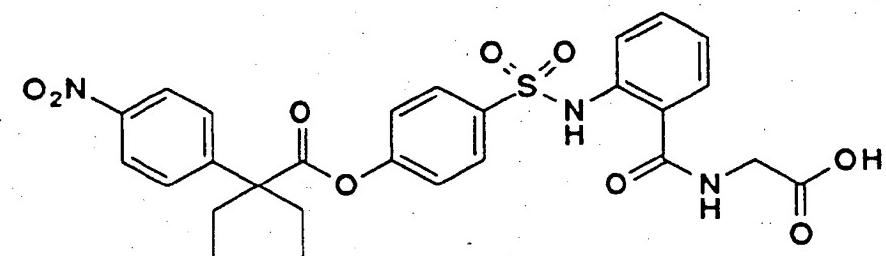


NMR (DMSO-d₆): δ 9.2-9.1 (1H, brt), 8.22 (2H, d, J=8Hz), 7.8-7.6 (5H, m), 7.5-7.4 (2H, m), 7.2-7.1 (3H, m), 3.88 (2H, d, J=5Hz), 2.8-2.6 (2H, m), 2.2-1.9 (2H, m), 1.9-1.6 (4H, m);
 TLC : Rf 0.20 (acetic acid:methanol:chloroform=1:2:40).

5 Example 2(178)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(4-nitrophenyl)-2-ethylbutanoic acid ester

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NMR (DMSO-d₆): δ 13.40-11.20 (2H, br), 9.35-9.15 (1H, m), 8.24 (2H, d, J=8Hz), 7.82 (2H, d, J=8Hz), 7.74 (1H, t, J=8Hz), 7.67 (2H, d, J=8Hz), 7.55-7.40 (2H, m), 7.23 (2H, d, J=8Hz), 7.19-7.08 (1H, m), 3.89 (2H, d, J=6Hz), 2.25-1.98 (4H, m), 0.76 (6H, t, J=7Hz);

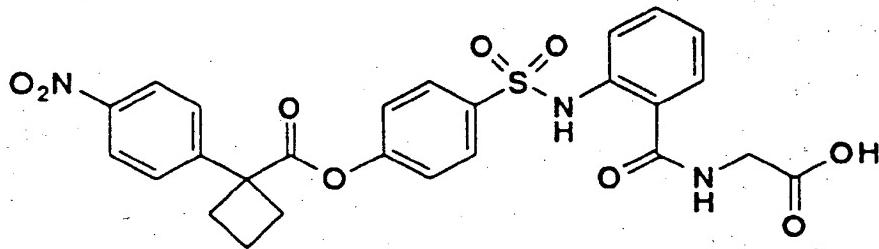
TLC : Rf 0.28 (acetic acid:methanol:chloroform=1:3:30).

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Example 2(179)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester

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NMR (DMSO-d₆): δ 9.2-9.1 (1H, brt), 8.24 (2H, d, J=8Hz), 7.8-7.6 (5H, m), 7.5-7.4 (2H, m), 7.3-7.1 (3H, m), 3.88 (2H, d, J=5Hz), 3.0-2.8 (2H, br), 2.7-2.5 (2H, m), 2.2-1.8 (2H, m);

TLC : Rf 0.22 (acetic acid:methanol:chloroform=1:2:40).

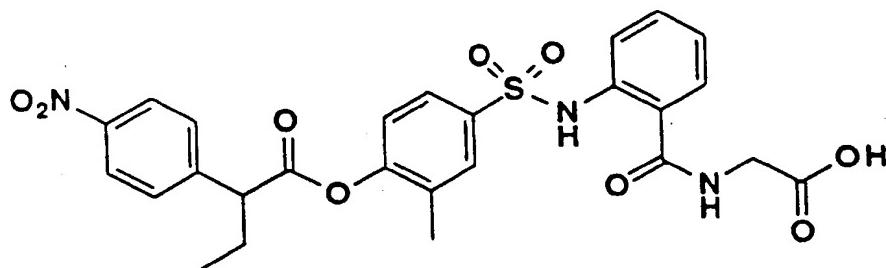
45

Example 2(180)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2-methylphenyl 2RS-(4-nitrophenyl)butanoic acid ester

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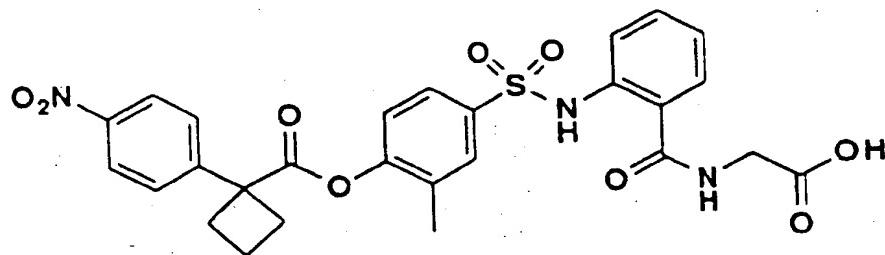
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15 NMR (DMSO-d₆): δ 13.00-12.40 (1H, br), 11.80-11.40 (1H, br), 9.19 (1H, t, J=5Hz), 8.24 (2H, d, J=8Hz), 7.80-7.55 (5H, m), 7.55-7.40 (2H, m), 7.23-7.06 (2H, m), 4.15 (1H, t, J=7Hz), 3.88 (2H, d, J=5Hz), 2.19 (1H, ddq, J=14Hz, 7Hz, 7Hz), 2.05-1.75 (4H, m), 0.88 (3H, t, J=7Hz);
TLC : Rf 0.20 (acetic acid:methanol:chloroform=1:2:20).

Example 2(181)

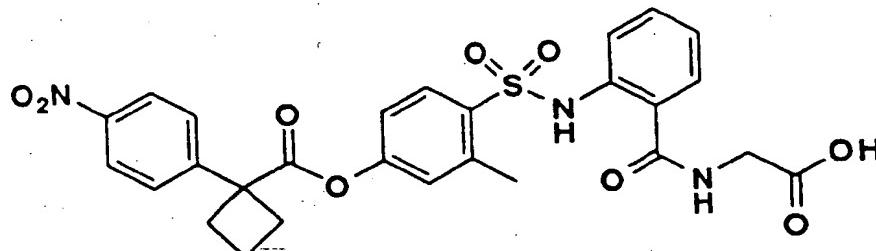
20 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2-methylphenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester



35 NMR (DMSO-d₆): δ 12.80-11.00 (2H, br), 9.20 (1H, t, J=5Hz), 8.24 (2H, d, J=8Hz), 7.80-7.55 (5H, m), 7.55-7.37 (2H, m), 7.25-7.05 (2H, m), 3.86 (2H, d, J=5Hz), 3.04-2.85 (2H, m), 2.74-2.54 (2H, m), 2.23-1.78 (5H, m);
TLC : Rf 0.20 (acetic acid:methanol:chloroform=1:2:40).

Example 2(182)

40 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-3-methylphenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester



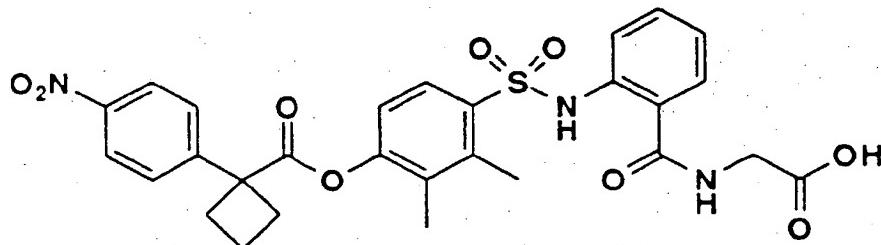
55 NMR (DMSO-d₆): δ 13.30-12.30 (1H, br), 12.00-11.56 (1H, br), 9.34-9.16 (1H, m), 8.26 (2H, d, J=8Hz), 7.85-7.65 (4H, m), 7.50-7.35 (2H, m), 7.22 (1H, d, J=8Hz), 7.18-7.05 (1H, m), 6.85 (1H, s), 3.97 (2H, d, J=5Hz), 3.22-3.03 (2H, m), 2.78-2.58 (2H, m), 2.28 (3H, s), 2.28-2.08 (1H, m), 2.05-1.80 (1H, m);
TLC : Rf 0.43 (acetic acid:methanol:chloroform=1:3:30).

EP 0 769 498 A1

Example 2(183)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2,3-dimethylphenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester

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NMR (DMSO-d₆): δ 13.10-12.40 (1H, br), 12.00-11.70 (1H, br), 9.35-9.22 (1H, m), 8.27 (2H, d, J=8Hz), 7.88-7.73 (3H, m), 7.65 (1H, d, J=8Hz), 7.51-7.39 (2H, m), 7.20 (1H, d, J=8Hz), 7.15-7.06 (1H, m), 4.08-3.95 (2H, m), 3.18-2.99 (1H, m), 2.99-2.78 (1H, m), 2.66-2.47 (1H, m), 2.33-2.05 (1H, m), 2.18 (3H, s), 2.05-1.82 (1H, m), 1.35 (3H, s);
TLC : Rf 0.43 (acetic acid:methanol:chloroform=1:3:30).

Example 2(184)

7-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2,3-dihydroinden-4-yl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester

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NMR (DMSO-d₆): δ 13.10-12.30 (1H, br), 12.00-11.46 (1H, br), 9.22 (1H, t, J=5Hz), 8.25 (2H, d, J=8Hz), 7.80-7.60 (4H, m), 7.50-7.34 (2H, m), 7.18-7.02 (2H, m), 3.90 (2H, d, J=5Hz), 3.14-2.78 (4H, m), 2.74-2.33 (4H, m), 2.20-1.78 (4H, m);
TLC : Rf 0.20 (acetic acid:methanol:chloroform=1:2:60).

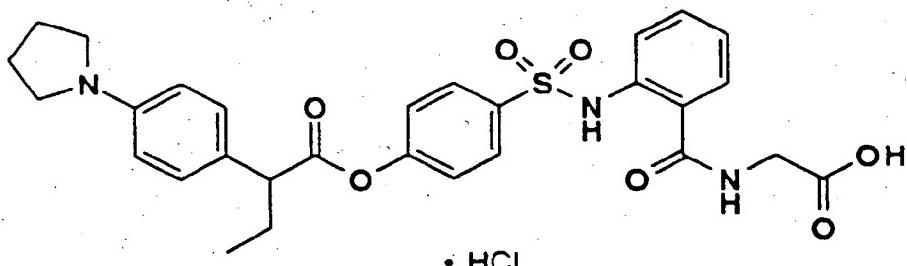
Example 2(185)

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4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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NMR (d_6 -DMSO): δ 11.60 (1H, s), 9.23 (1H, t, $J=6$ Hz), 7.85-7.70 (3H, m), 7.55-7.40 (2H, m), 7.27-7.08 (5H, m), 6.80-6.55 (2H, m), 3.88 (2H, d, $J=6$ Hz), 3.68 (1H, t, $J=7$ Hz), 3.38-3.19 (4H, m), 2.20-1.86 (5H, m), 1.86-1.62 (1H, m), 0.86 (3H, t, $J=7$ Hz);

TLC : Rf 0.44 (chloroform:methanol:acetic acid=30:2:1).

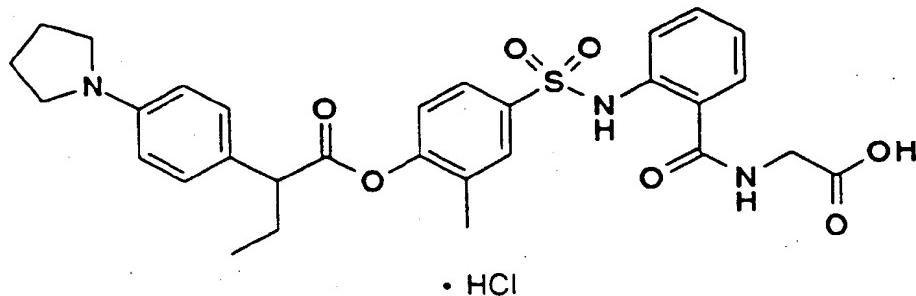
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Example 2(186)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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NMR (DMSO-d₆): δ 11.56 (1H, s), 9.23 (1H, t, $J=5$ Hz), 7.83-7.55 (3H, m), 7.55-7.40 (2H, m), 7.30-7.05 (4H, m), 6.84-6.60 (2H, m), 3.88 (2H, d, $J=5$ Hz), 3.70 (1H, t, $J=7$ Hz), 3.40-3.13 (4H, m), 2.20-1.65 (9H, m), 0.86 (3H, t, $J=7$ Hz);

TLC : Rf 0.45 (acetic acid:methanol:chloroform=1:3:30).

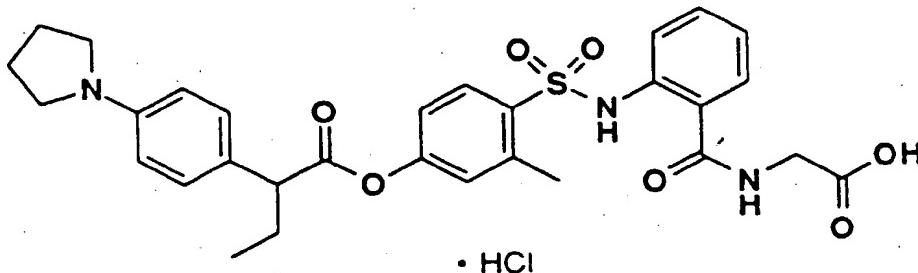
Example 2(187)

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4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-3-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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NMR (DMSO-d₆): δ 12.20 (1H, s), 9.28 (1H, t, $J=5$ Hz), 7.85 (2H, d, $J=8$ Hz), 7.50-7.35 (2H, m), 7.30-7.18 (3H, m), 7.18-7.03 (1H, m), 6.80 (1H, s), 6.73 (2H, d, $J=8$ Hz), 4.00 (2H, d, $J=5$ Hz), 3.93-3.75 (1H, m), 3.38-3.20 (4H, m), 2.28 (3H, s), 2.20-2.00 (1H, m), 2.03-1.92 (4H, m), 1.92-1.65 (1H, m), 0.88 (3H, t, $J=7$ Hz);

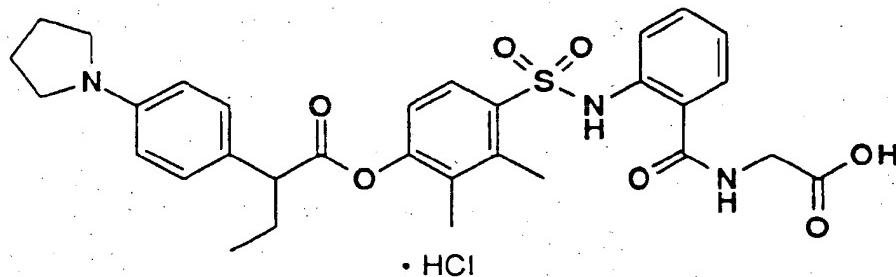
TLC : Rf 0.41 (acetic acid:methanol:chloroform=1:3:30).

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Example 2(188)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2,3-dimethylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

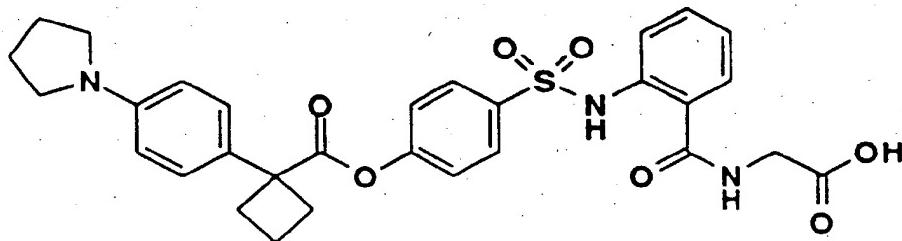
55



15 NMR (DMSO-d₆): δ 12.09 (1H, s), 9.35-9.18 (1H, m), 7.92-7.77 (1H, m), 7.77-7.63 (1H, m), 7.46-7.38 (2H, m), 7.30-7.17 (3H, m), 7.17-7.03 (1H, m), 6.86-6.60 (2H, m), 4.02 (2H, d, J=5Hz), 3.93-3.80 (1H, m), 3.40-3.15 (4H, m), 2.19 (3H, s), 2.05-1.90 (4H, m), 1.90-1.50 (1H, m), 1.45 (3H, s), 1.30-0.98 (1H, m), 0.88 (3H, t, J=7Hz);
TLC : Rf 0.40 (acetic acid:methanol:chloroform=1:3:30).

20 Example 2(189)

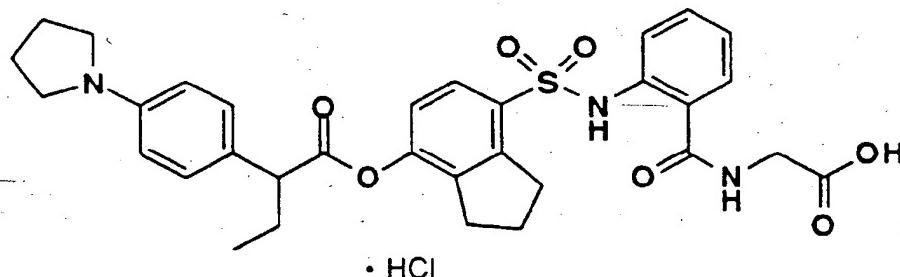
25 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-(pyrrolidin-1-yl)phenyl)cyclobutanecarboxylic acid ester



35 NMR (CD₃OD): δ 7.75-7.50 (4H, m), 7.50-7.25 (3H, m), 7.20-6.90 (5H, m), 3.92 (2H, s), 3.46 (4H, brs), 2.90 (2H, m), 2.56 (2H, m), 2.25-1.85 (6H, m);
TLC : Rf 0.36 (acetic acid:methanol:chloroform=1:3:30).

40 Example 2(190)

45 7-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2,3-dihydroinden-4-yl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



NMR (DMSO-d₆): δ 11.69 (1H, s), 9.24 (1H, t, J=5Hz), 7.75 (1H, d, J=8Hz), 7.69 (1H, d, J=8Hz), 7.50-7.38 (2H,

EP 0 769 498 A1

m), 7.19 (2H, d, J=8Hz), 7.15-7.04 (1H, m), 6.98 (1H, d, J=8Hz), 6.68 (2H, d, J=8Hz), 3.89 (2H, d, J=5Hz), 3.66 (1H, t, J=5Hz), 3.35-3.15 (4H, m), 3.15-3.00 (2H, m), 2.55-2.40 (2H, m), 2.18-1.85 (7H, m), 1.85-1.60 (1H, m), 0.86 (3H, t, J=7Hz);

TLC : Rf 0.34 (acetic acid:methanol:chloroform=1:3:30).

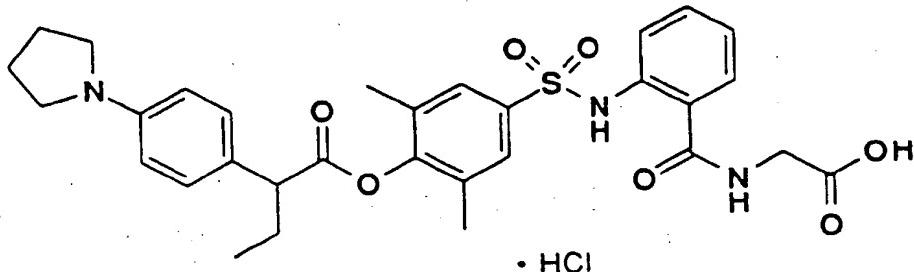
5

Example 2(191)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2,6-dimethylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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NMR (DMSO-d₆): δ 11.49 (s, 1H), 9.3-9.2 (m, 1H), 7.8-7.1 (m, 10H), 6.8-6.6 (m, 1H), 4.0-3.7 (m, 3H), 3.4-3.1 (m, 4H), 2.2-1.7 (m, 12H), 0.89 (t, J=7.0Hz, 3H);

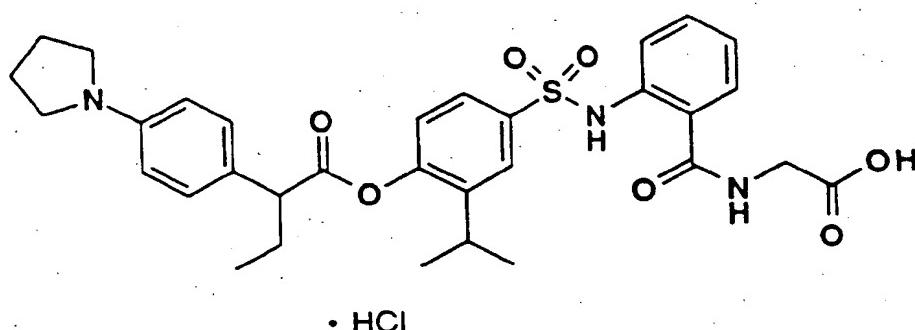
25 TLC : Rf 0.60 (chloroform:methanol=2:1).

Example 2(192)

30 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2-isopropylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

35

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45

50 NMR (CDCl₃): δ 10.04 (s, 1H), 7.8-7.7 (m, 3H), 7.6-7.5 (m, 7H), 7.2-7.1 (m, 1H), 6.9-6.8 (m, 1H), 6.4-6.3 (m, 1H), 4.0-3.6 (m, 7H), 2.8-2.7 (m, 1H), 2.4-2.2 (m, 5H), 2.0-1.8 (m, 1H), 0.98 (t, J=7.0Hz, 3H), 0.91 (d, J=7.0Hz, 6H);

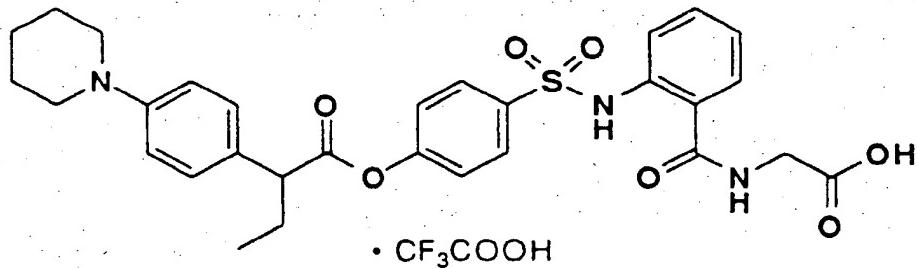
TLC : Rf 0.61 (chloroform:methanol=2:1).

55

Example 2(193)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(piperidin-1-yl)phenyl)butanoic acid ester · trifluoroacetate

55



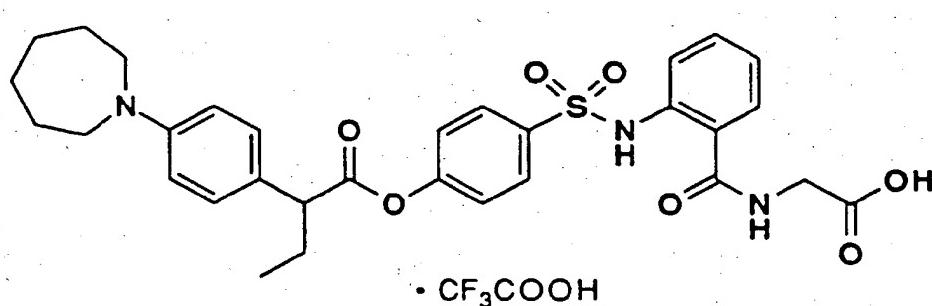
¹⁵ NMR (d_6 -DMSO): δ 12.60-11.50 (1H, br), 9.43-9.23 (1H, br), 7.83-7.68 (3H, m), 7.52-7.35 (2H, m), 7.30-7.02 (5H, m), 6.88 (2H, d, J =8Hz), 3.88 (2H, d, J =7Hz), 3.66 (1H, t, J =8Hz), 3.20-3.05 (4H, m), 2.15-1.91 (1H, m), 1.85-1.43 (7H, m), 0.93 (3H, t, J =7Hz);

TLC : Rf 0.28 (chloroform:methanol:acetic acid=30:3:1).

Example 2(194)

20

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(perhydroazepin-1-yl)phenyl)butanoic acid ester · trifluoroacetate

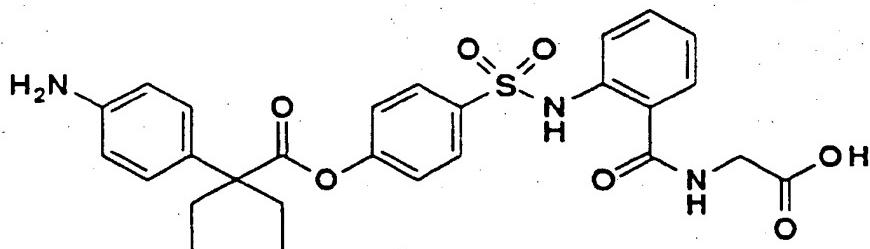


⁴⁰ NMR (DMSO-d₆): δ 11.57 (1H, s), 9.19 (1H, t, J=7Hz), 7.85-7.65 (3H, m), 7.55-7.40 (2H, m), 7.30-7.05 (5H, m), 6.64 (2H, d, J=8Hz), 3.88 (2H, d, J=7Hz), 3.60 (1H, t, J=8Hz), 3.48-3.28 (4H, m), 2.10-1.93 (1H, m), 1.88-1.55 (5H, m), 1.55-1.30 (4H, m), 0.86 (3H, t, J=7Hz);

TLC : Rf 0.35 (acetic acid:methanol:chloroform=1:3:30).

Example 2(195)

45 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(4-aminophenyl)-2-ethylbutanoic acid ester



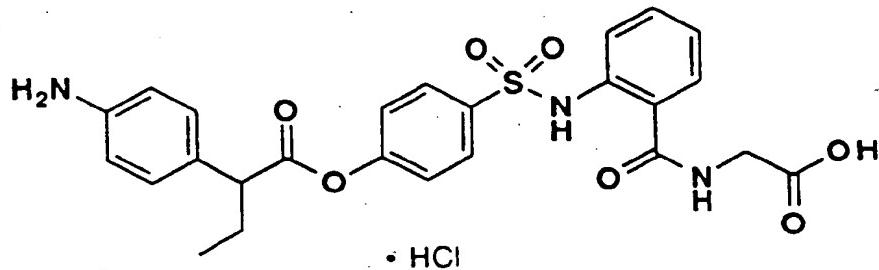
EP 0 769 498 A1

NMR (DMSO-d₆): δ 11.58 (1H, br), 9.22 (1H, t, J=5Hz), 7.80-7.70 (3H, m), 7.53-7.42 (2H, m), 7.18-7.14 (3H, m), 6.98 (2H, d, J=8Hz), 6.56 (2H, d, J=8Hz), 3.89 (2H, d, J=6Hz), 2.09-1.88 (4H, m), 0.74 (6H, t, J=7Hz);
 TLC : Rf 0.40 (acetic acid:methanol:chloroform=1:3:30).

5 Example 2(196)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-aminophenyl)butanoic acid ester · hydrochloride

10

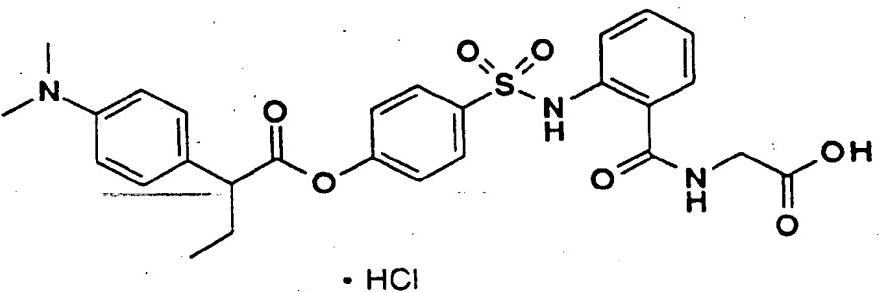


NMR (DMSO-d₆): δ 10.65 (1H, br), 7.83-7.76 (3H, m), 7.31-6.96 (6H, m), 6.80-6.73 (1H, m), 6.53 (2H, d, J=8.6Hz), 3.86 (2H, d-like), 3.55 (1H, t, J=7.4Hz), 2.12-1.90 and 1.83-1.62 (each 1H, m), 0.87 (3H, t, J=7.0Hz);
 TLC : Rf 0.16 (chloroform:methanol:water=8:2:0.2).

Example 2(197)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(N,N-dimethylamino)phenyl)butanoic acid ester · hydrochloride

35



NMR (DMSO-d₆): δ 11.62 (1H, s), 9.25 (1H, t, J=6Hz), 7.80 (2H, d, J=9Hz), 7.76 (1H, d, J=8Hz), 7.50-7.44 (5H, m), 7.27-7.14 (4H, m), 3.89 (2H, d, J=6Hz), 3.86 (1H, t, J=8Hz), 3.04 (6H, s), 2.17-2.03 and 1.91-1.71 (each 1H, m), 0.88 (3H, t, J=7Hz);

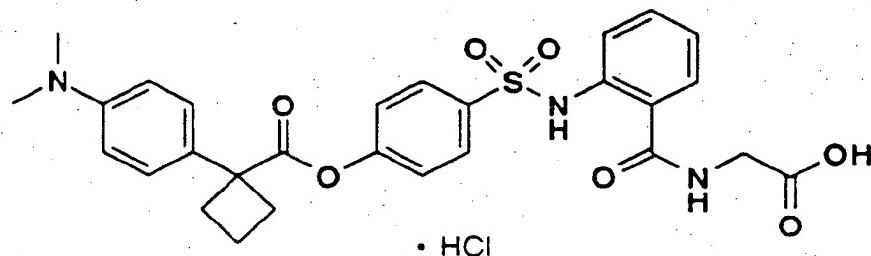
TLC : Rf 0.48 (acetic acid:methanol:chloroform=1:3:30).

50

Example 2(198)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-(N,N-dimethylamino)phenyl)cyclobutanecarboxylic acid ester · hydrochloride

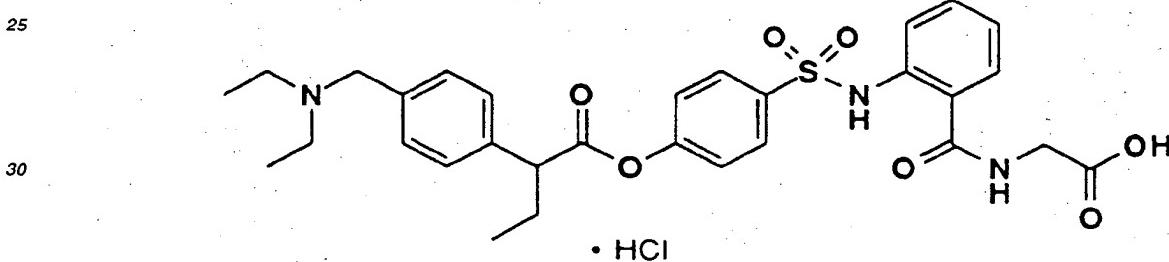
55



15 NMR (DMSO-d₆): δ 11.62 (1H, s), 9.24 (1H, t-like), 7.79 (2H, d, J=8.8Hz), 7.74 (1H, d, J=8.0Hz), 7.81-7.70 (9H, m), 3.89 (2H, d, J=5.0Hz), 3.02 (6H, s), 2.93-2.80 (2H, m), 2.59-2.39 (2H, m), 2.09-1.81 (2H, m);
TLC : Rf 0.26 (chloroform:methanol:water=8:2:0.2).

Example 2(199)

20 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(N,N-diethylaminomethyl)phenyl)butanoic acid ester · hydrochloride

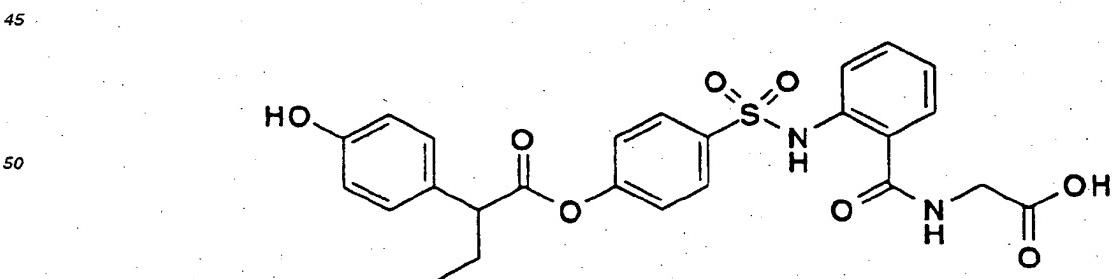


NMR (DMSO-d₆): δ 13.00-11.00 (2H, br), 9.35-9.18 (1H, m), 7.90-7.71 (3H, m), 7.68-7.56 (2H, m), 7.56-7.38 (4H, m), 7.30-7.08 (3H, m), 4.24 (2H, s), 3.99-3.79 (2H, m), 3.71-3.65 (1H, m), 3.10-2.90 (4H, m), 2.11 (1H, ddq, J=14Hz, 7Hz, 7Hz), 1.82 (1H, ddq, J=14Hz, 7Hz, 7Hz), 1.23 (6H, t, J=7Hz), 0.88 (3H, t, J=7Hz);
TLC : Rf 0.18 (acetic acid:methanol:chloroform=1:2:20).

40

Example 2(200)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-hydroxyphenyl)butanoic acid ester

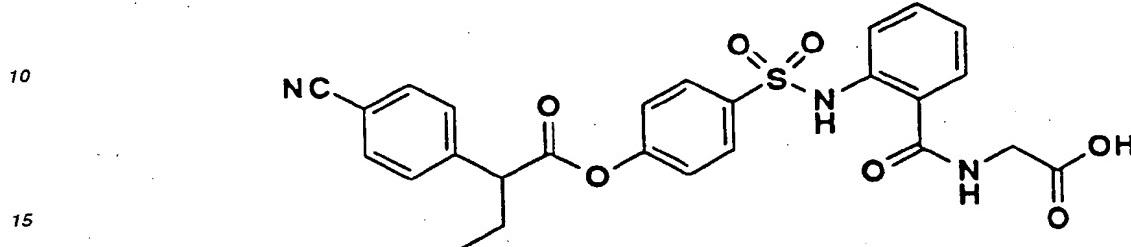


55 NMR (DMSO-d₆): δ 12.90-11.20 (2H, br), 9.39 (1H, br), 9.22 (1H, t-like), 7.79 (2H, d, J=8.8Hz), 7.73 (1H, d, J=7.8Hz), 7.53-7.42 (2H, m), 7.19-7.12 (5H, m), 6.74 (2H, d, J=8.6Hz), 3.89 (2H, d, J=5.6Hz), 3.68 (1H, t, J=7.6Hz), 2.11-1.93 and 1.84-1.62 (each 1H, m), 0.86 (3H, t, J=7.2Hz);

TLC : Rf 0.12 (chloroform:methanol:water=8:2:0.2).

Example 2(201)

5 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-cyanophenyl)butanoic acid ester

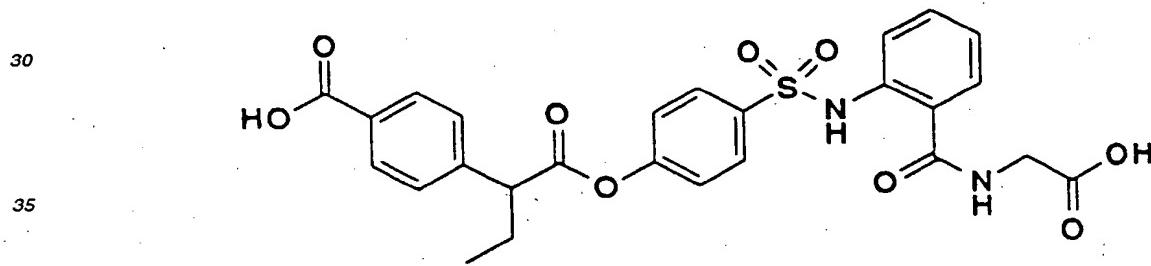


20 NMR (DMSO-d₆): δ 10.72-10.41 (1H, m), 7.88-7.69 (5H, m), 7.59 (2H, d, J=8.2Hz), 7.29 (2H, d, J=8.2Hz),
7.22-7.06 (3H, m), 6.78 (1H, t, J=8.2Hz), 4.01 (1H, t, J=7.4Hz), 3.91-3.77 (2H, m), 2.24-2.01 and 1.95-1.70 (each 1H,
m), 0.88 (3H, t, J=7.4Hz);

TLC : Rf 0.24 (chloroform:methanol:water=8:2:0.2).

Example 2(202)

25 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-carboxyphenyl)butanoic acid ester

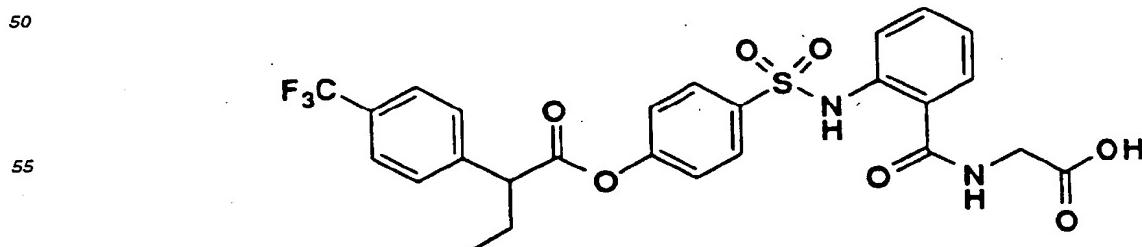


40 NMR (DMSO-d₆): δ 11.36 (1H, s), 10.45 (1H, s), 9.16 (1H, t-like), 7.90 (2H, d, J=8Hz), 7.71 (1H, d, J=8Hz),
7.60-7.38 (7H, m), 7.18-7.03 (1H, m), 6.81 (2H, d, J=8Hz), 3.89 (2H, d, J=6Hz), 3.40 (1H, t, J=7Hz), 2.04-1.58 (2H,
m), 0.83 (3H, t, J=7Hz);

TLC : Rf 0.53 (acetic acid:methanol:chloroform=1:5:15).

45 Example 2(203)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-trifluoromethylphenyl)butanoic acid ester



NMR (DMSO-d₆): δ 10.75-10.45 (1H, m), 7.87-7.56 (7H, m), 7.35-7.07 (4H, m), 6.87-6.72 (1H, m), 4.02 (1H, t, J=7.7Hz), 3.93-3.82 (2H, m), 2.25-2.02 and 1.95-1.71 (each 1H, m), 0.89 (3H, t, J=7.0Hz);
TLC : Rf 0.23 (chloroform:methanol:water=8:2:0.2).

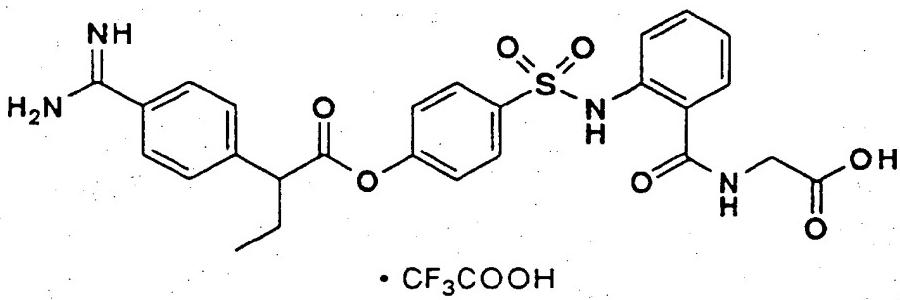
5 Example 2(204)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-amidinophenyl)butanoic acid ester · trifluoroacetate

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NMR (DMSO-d₆): δ 10.42-10.20 (1H, m), 9.95-9.44 (2H, m), 9.44-8.90 (2H, m), 7.86-7.66 (4H, m), 7.66-7.30 (4H, m), 7.30-7.04 (3H, m), 6.88-6.75 (1H, m), 4.01 (1H, t, J=7Hz), 3.90-3.79 (2H, m), 2.26-2.03 (1H, m), 1.95-1.74 (1H, m), 0.96-0.76 (3H, m);

TLC : Rf 0.40 (acetic acid:methanol:chloroform=1:2:10).

Example 2(205)

30

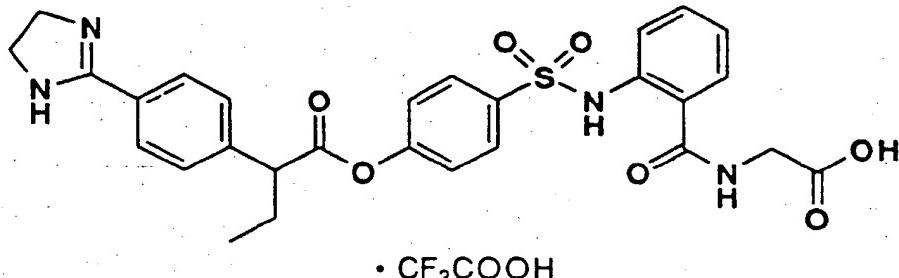
4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(imidazolin-2-yl)phenyl)butanoic acid ester · trifluoroacetate

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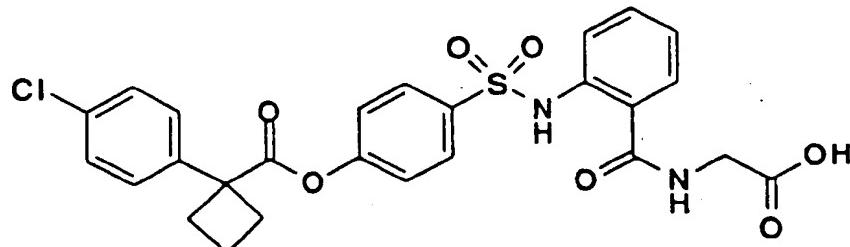
NMR (DMSO-d₆): δ 10.60-10.34 (1H, m), 7.95 (2H, d, J=8Hz), 7.82-7.71 (3H, m), 7.64 (2H, d, J=8Hz), 7.34 (1H, d, J=8Hz), 7.26-7.00 (4H, m), 6.80 (1H, t, J=8Hz), 4.60-3.93 (7H, m), 2.15 (1H, ddq, J=14Hz, 7Hz, 7Hz), 1.94-1.71 (1H, m), 0.87 (3H, t, J=7Hz);

TLC : Rf 0.2 (acetic acid:methanol:chloroform=1:2:10).

Example 2(206)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-chlorophenyl)cyclobutanecarboxylic acid ester

55

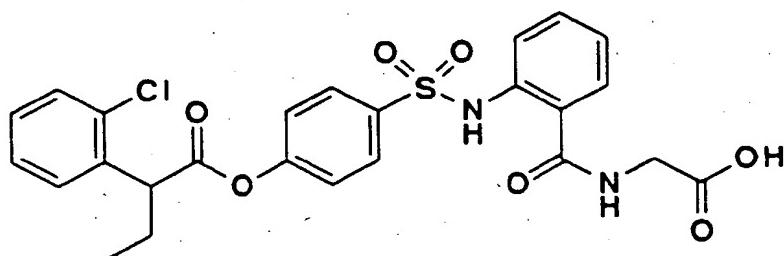


NMR (DMSO-d_6): δ 9.3-9.1 (1H, brt), 7.8-7.6 (3H, m), 7.5-7.3 (6H, m), 7.2-7.0 (3H, m), 3.88 (2H, d, $J=5\text{Hz}$), 3.0-2.8 (2H, m), 2.6-2.4 (2H, m), 2.2-1.8 (2H, m);
TLC: R_f 0.28 (acetic acid:methanol:water, 1:2:10)

TLC : Rf 0.22 (acetic acid:methanol:chloroform=1:2:40).

Example 2(207)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(2-chlorophenyl)butanoic acid ester

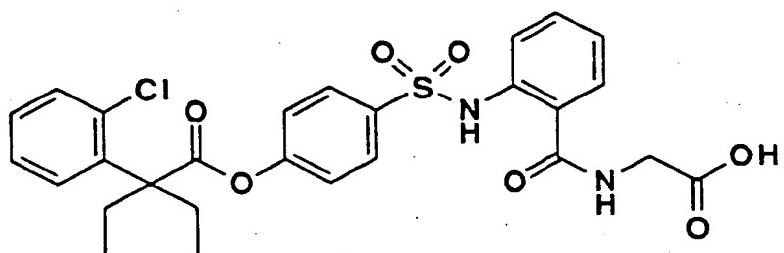


NMR (DMSO-d₆): δ 9.4-9.2 (1H, br), 7.8-7.7 (3H, m), 7.5-7.3 (6H, m), 7.3-7.0 (3H, m), 4.24 (1H, t, J=7Hz), 3.88 (2H, d, J=5Hz), 2.2-2.0 (1H, m), 2.0-1.8 (1H, m), 0.87 (3H, t, J=7Hz);

TLC : Rf 0.16 (acetic acid:methanol:chloroform=1:2:40).

Example 2(208)

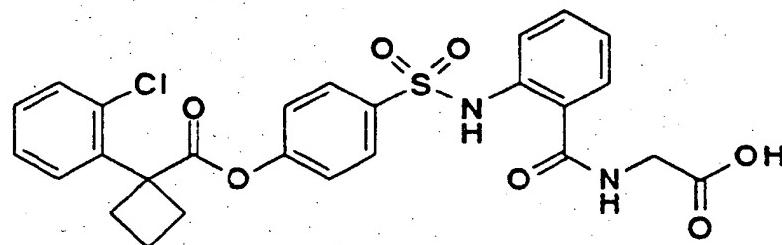
4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(2-chlorophenyl)-2-ethylbutanoic acid ester



NMR (DMSO-d_6): δ 9.5-9.3 (1H, br), 7.82 (2H, d, $J=8\text{Hz}$), 7.72 (1H, d, $J=8\text{Hz}$), 7.6-7.3 (6H, m), 7.23 (2H, d, $J=8\text{Hz}$), 7.09 (1H, t, $J=8\text{Hz}$), 3.90 (2H, d, $J=5\text{Hz}$), 2.4-2.1 (2H, m), 2.2-1.9 (2H, m), 0.70 (6H, t, $J=7\text{Hz}$);
TLC: R_f 0.12 (acetic acid:methanol:chloroform=1:2:40).

Example 2(209)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(2-chlorophenyl)cyclobutanecarboxylic acid ester



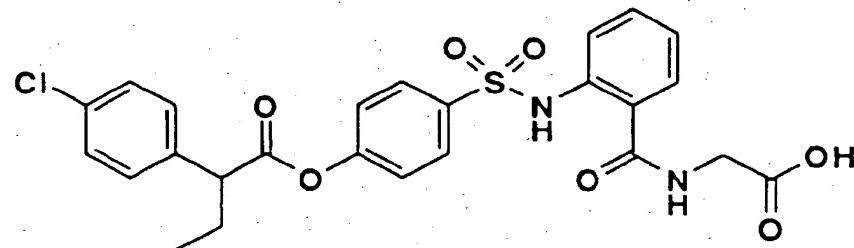
NMR ($\text{CDCl}_3+\text{CD}_3\text{OD}$): δ 7.72 (2H, d, $J=8.5\text{Hz}$), 7.68-7.05 (8H, m), 7.02 (2H, d, $J=8.5\text{Hz}$), 3.99 (2H, s), 3.01-2.82 (2H, m), 2.75-2.50 (2H, m), 2.41-2.15 (1H, m), 2.10-1.80 (1H, m);
TLC : Rf 0.30 (acetic acid:methanol:chloroform=1:2:40).

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Example 2(210)

4-(N-2-(N'-carboxymethyl)carbamoyl)phenylsulfamoylphenyl 2RS-(4-chlorophenyl)butanoic acid ester

20



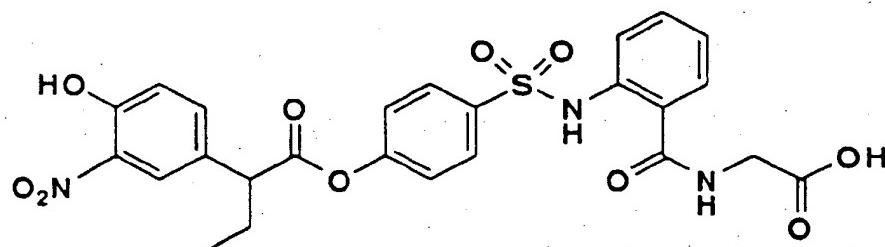
NMR (DMSO-d_6): δ 10.47-10.18 (1H, m), 7.86-7.74 (3H, m), 7.51-7.08 (8H, m), 6.93-6.81 (1H, m), 3.95-3.82 (3H, m), 2.20-1.96 and 1.90-1.66 (each 1H, m), 0.87 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.26 (chloroform:methanol:water=8:2:0.2).

35

Example 2(211)

4-(N-2-(N'-carboxymethyl)carbamoyl)phenylsulfamoylphenyl 2RS-(3-nitro-4-hydroxyphenyl)butanoic acid ester

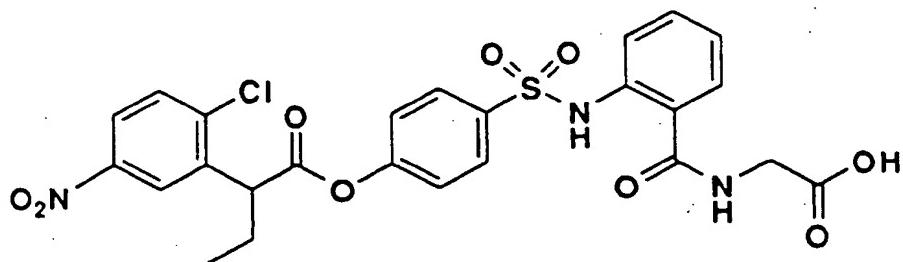
40



NMR (DMSO-d_6): δ 9.36 (1H, t-like), 7.90-7.72 (4H, m), 7.58-7.40 (3H, m), 7.24-7.07 (4H, m), 3.90 (2H, d, $J=6\text{Hz}$), 2.20-1.97 and 1.89-1.69 (each 1H, m), 0.88 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.21 (acetic acid:methanol:chloroform=1:2:40).

55 Example 2(212)

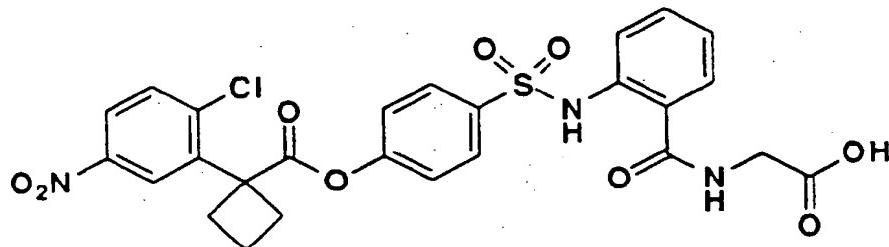
4-(N-2-(N'-carboxymethyl)carbamoyl)phenylsulfamoylphenyl 2RS-(2-chloro-5-nitrophenyl)butanoic acid ester



15 NMR(DMSO-d₆): δ 12.10 (2H, br), 9.26 (1H, t-like), 8.32 (1H, t, J=3Hz), 8.20 (1H, dd, J=3 and 9Hz), 7.85-7.79 (3H, m), 7.73 (1H, d, J=8Hz), 7.52-7.41 (2H, m), 7.27 (2H, d, J=9Hz), 7.15-7.08 (1H, m), 4.43 (1H, t, J=6Hz), 3.89 (2H, d, J=6Hz), 2.32-2.18 and 2.09-1.91 (each 1H, m), 0.90 (3H, t, J=7Hz);
TLC : Rf 0.51 (acetic acid:methanol:chloroform=1:3:30).

Example 2(213)

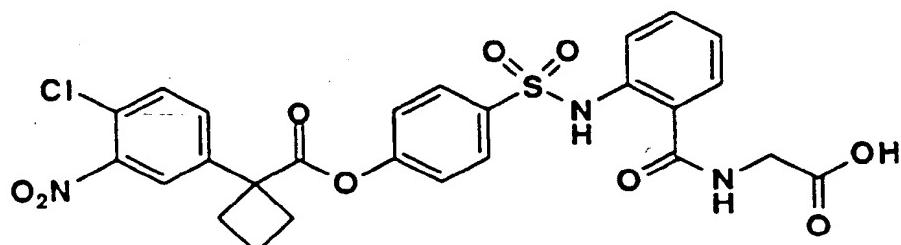
20 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(2-chloro-5-nitrophenyl)cyclobutanecarboxylic acid ester



35 NMR (CDCl₃+CD₃OD): δ 8.32 (1H, d, J=2.5Hz), 8.14 (1H, dd, J=2.5, 8.5Hz), 7.76 (2H, d, J=8.5Hz), 7.62 (2H, t, J=8.5Hz), 7.53 (1H, d, J=8.5Hz), 7.43 (1H, d, J=8.5Hz), 7.12 (1H, d, J=8.5Hz), 7.06 (2H, d, J=8.5Hz), 3.99 (2H, brs), 3.10-2.90 (2H, m), 2.80-2.59 (2H, m), 2.52-2.20 (1H, m), 2.15-1.90 (1H, m);
TLC : Rf 0.23 (acetic acid:methanol:chloroform=1:2:40).

Example 2(214)

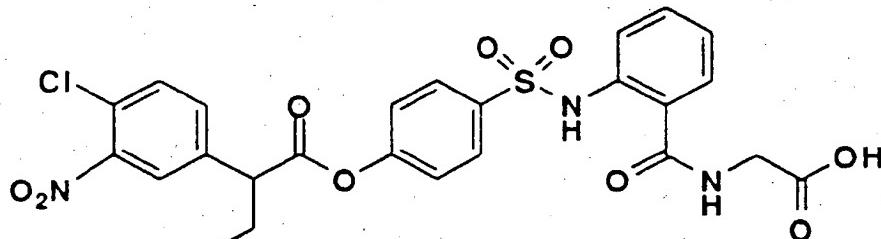
40 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(3-nitro-4-chlorophenyl)cyclobutanecarboxylic acid ester



55 NMR (DMSO-d₆): δ 12.73 (1H, brs), 11.60 (1H, brs), 9.17 (1H, t, J=7Hz), 8.04 (1H, s), 7.90-7.65 (4H, m), 7.55-7.40 (2H, m), 7.35-7.05 (4H, m), 3.90 (2H, d, J=7Hz), 2.90 (2H, m), 2.60 (2H, m), 2.25-1.80 (2H, m);
TLC : Rf 0.34 (acetic acid:methanol:chloroform=1:3:30).

Example 2(215)

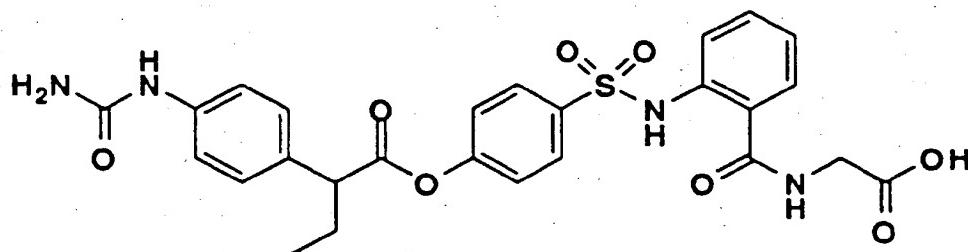
4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(3-nitro-4-chlorophenyl)butanoic acid ester



NMR (DMSO-d₆): δ 10.79 (1H, br), 8.12 (1H, s), 7.85-7.75 (5H, m), 7.28-7.08 (4H, m), 6.74 (1H, t-like), 4.08 (1H, t, J=7.4Hz), 3.84 (2H, d-like), 2.22-2.04 and 1.98-1.76 (each 1H, m), 0.89 (3H, t, J=7.2Hz);
TLC : Rf 0.30 (chloroform:methanol:water=8:2:0.2).

Example 2(216)

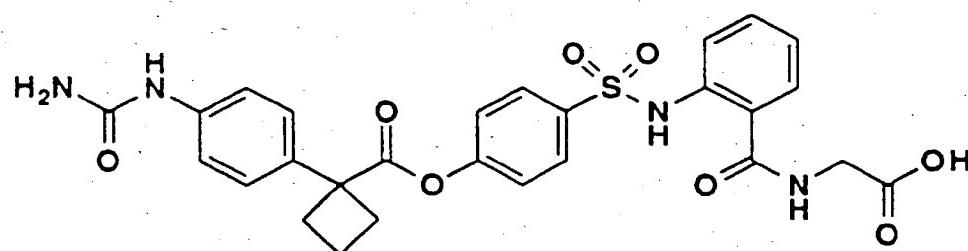
4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-ureidophenyl)butanoic acid ester



NMR (DMSO-d₆): δ 10.5 (1H, br), 8.61 (1H, s), 7.81-7.70 (3H, m), 7.41-7.05 (10H, m), 6.80 (1H, t, J=7.6Hz), 5.85 (2H, s), 3.84 (2H, s), 3.70 (1H, t, J=7.2Hz), 2.30 (2H, s), 2.60-1.95 and 1.90-1.65 (each 1H, m), 0.88 (3H, t, J=7.0Hz);
TLC : Rf 0.22 (acetic acid:methanol:chloroform=1:3:30).

Example 2(217)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-ureidophenyl)cyclobutanecarboxylic acid ester

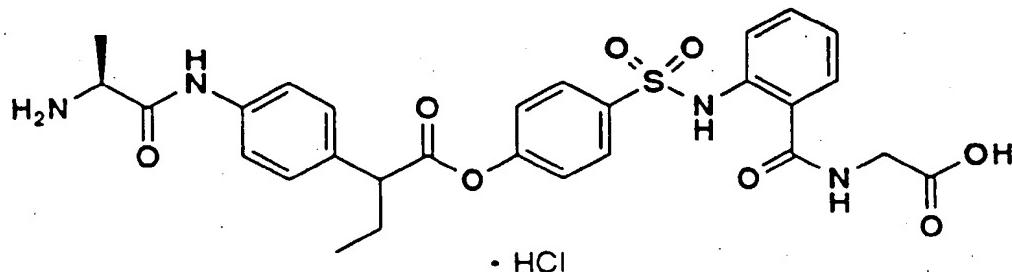


NMR (DMSO-d₆): δ 10.0 (1H, brs), 8.50 (1H, s), 7.67 (4H, d, J=8.8Hz), 7.32-7.09 (2H, m), 7.30 (2H, d, J=8.6Hz), 7.11 (2H, d, J=8.8Hz), 6.96 (2H, d, J=8.6Hz), 6.76 (1H, t, J=6.8Hz), 5.74 (2H, s), 3.75-3.73 (2H, m), 2.80-2.63 (2H, m), 2.53-2.26 (2H, m), 2.23-2.00 (2H, m);
TLC : Rf 0.10 (chloroform:methanol:acetic acid=40:2:1).

Example 2(218)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(N-(2S-aminopropionyl)amino)phenyl)butanoic acid ester · hydrochloride

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NMR (DMSO-d₆): δ 10.92 (1H, s), 9.47-9.32 (1H, m), 7.85-7.73 (3H, m), 7.66 (2H, d, J=9Hz), 7.54-7.42 (2H, m), 7.34 (2H, d, J=9Hz), 7.27-7.04 (4H, m), 4.16-3.99 (1H, m), 3.89 (2H, d, J=5Hz), 3.81 (1H, t, J=6Hz), 2.19-1.98 and 1.88-1.67 (each 1H, m), 1.47 (3H, d, J=8Hz), 0.97 (3H, t, J=8Hz);

TLC : R_f 0.11 (chloroform:methanol:water=8:2:0.2).

Example 2(219)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(N-(2S-amino-3-methylbutyl)amino)phenyl)butanoic acid ester · hydrochloride

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NMR (DMSO-d₆): δ 10.96-10.85 (1H, m), 9.45-9.30 (1H, m), 7.85-7.72 (2H, m), 7.66 (2H, d, J=8.4Hz), 7.54-7.42 (2H, m), 7.34 (2H, d, J=8.4Hz), 7.27-7.06 (4H, m), 3.90 (2H, d, J=6.0Hz), 3.81 (1H, t, J=7.8Hz), 2.33-1.98 and 1.92-1.66 (each 1H, m), 1.01 (6H, d, J=7.2Hz), 0.87 (3H, t, J=7.4Hz);

TLC : R_f 0.19 (chloroform:methanol:water=8:2:0.2).

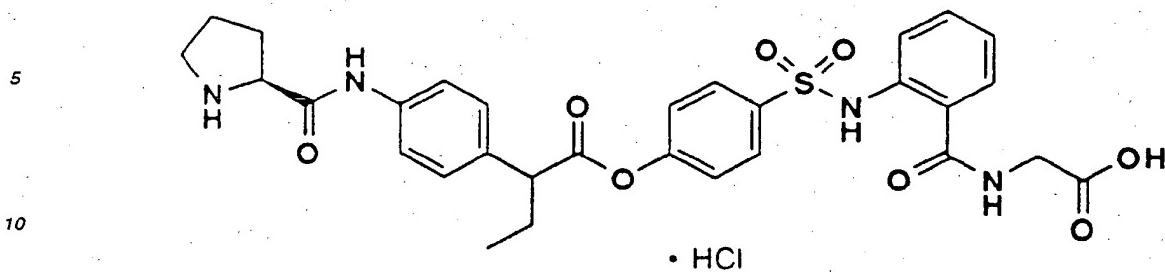
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Example 2(220)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(N-(pyrrolidin-2S-ylcarbonyl)amino)phenyl)butanoic acid ester · hydrochloride

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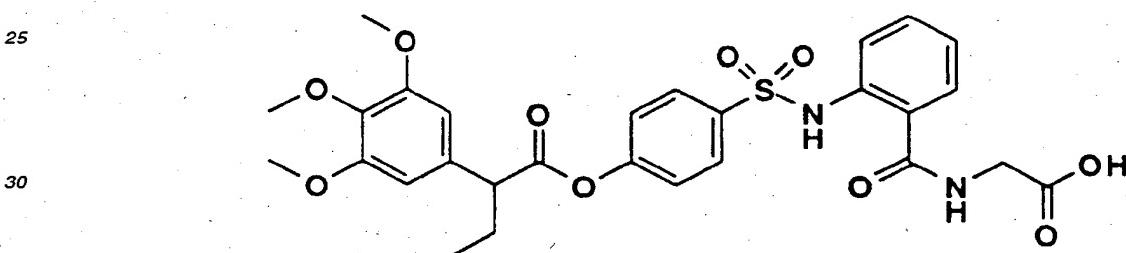
55



15 NMR (DMSO-d₆): δ 10.62-10.52 (1H, m), 9.95-9.70 (1H, m), 7.86-7.70 (3H, m), 7.62 (2H, d, J=8.8Hz), 7.48-7.27 (4H, m), 7.13 (2H, d, J=8.8Hz), 7.04-6.93 (1H, m), 4.34-4.20 (1H, m), 3.95-3.85 (2H, m), 3.81 (1H, t, J=7.1Hz), 3.33-3.16 (2H, m), 2.45-2.21 (1H, m), 2.21-1.68 (5H, m), 0.77 (3H, t, J=7.1Hz);
TLC : R_f 0.09 (chloroform:methanol:water=8:2:0.2).

20 Example 2(221)

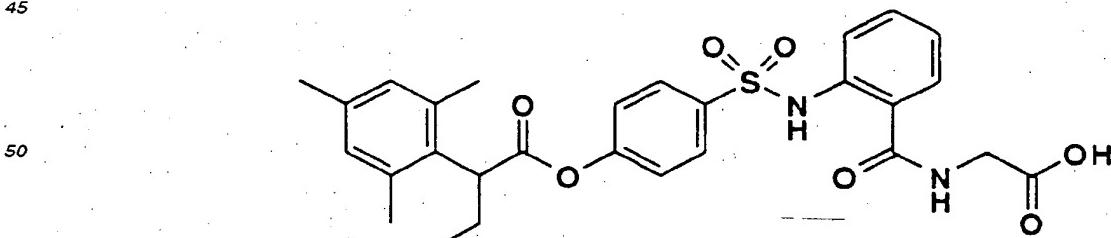
25 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(3,4,5-trimethoxyphenyl)butanoic acid ester



35 NMR (DMSO-d₆): δ 12.71 (1H, br), 11.69 (1H, br), 9.22 (1H, t-like), 7.80 (2H, d, J=8Hz), 7.73 (1H, d, J=8Hz), 7.53-7.41 (2H, m), 7.25-7.09 (3H, m), 6.63 (2H, s), 3.89 (2H, d, J=5Hz), 3.77 (6H, s), 3.65 (3H, s), 3.63 (1H, t, J=7Hz);
TLC : R_f 0.57 (acetic acid:methanol:chloroform=1:3:30).

40 Example 2(222)

45 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(2,4,6-trimethylphenyl)butanoic acid ester



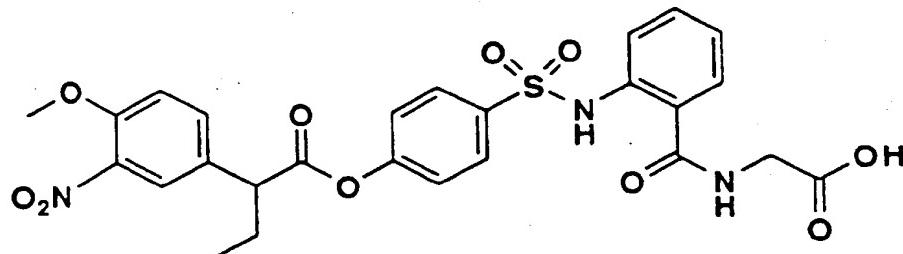
55 NMR (CD₃OD): δ 7.80-6.80 (12H, m), 4.21 (1H, dd, J=8.0 and 6.0Hz), 3.93 (2H, s), 2.30-2.20 (each 3H, s), 1.90-1.60 (2H, m), 0.90 (3H, t, J=7.2Hz);
TLC : R_f 0.46 (acetic acid:methanol:chloroform=1:3:30).

Example 2(223)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(3-nitro-4-methoxyphenyl)butanoic acid ester

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NMR (DMSO-d₆): δ 12.72 (1H, br), 11.60 (1H, br), 9.18 (1H, t-like), 7.89-7.59 (5H, m), 7.53-7.46 (2H, m), 7.36 (1H, d, J=9Hz), 7.24 (2H, d, J=9Hz), 7.13 (1H, t, J=8Hz), 3.95 (1H, t, J=8Hz), 3.92 (3H, s), 3.89 (2H, d, J=6Hz), 2.23-2.02 and 1.94-1.72 (each 1H, m), 0.88 (3H, t, J=7Hz);

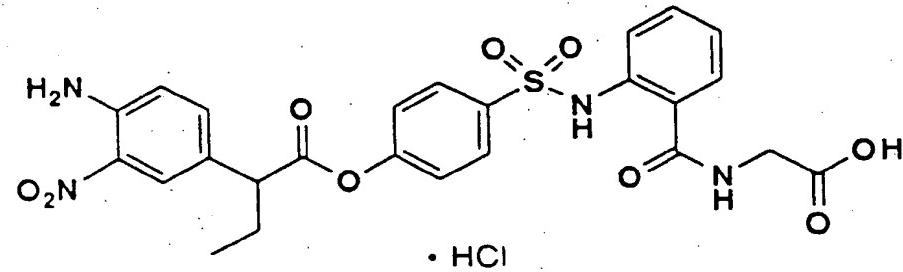
TLC : RI 0.51 (acetic acid:methanol:chloroform=1:3:30).

Example 2(224)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(3-nitro-4-aminophenyl)butanoic acid ester
hydrochloride

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NMR (DMSO-d₆): δ 12.14 (2H, br), 9.36 (1H, t-like), 7.95 (1H, d, J=2.0Hz), 7.79 (2H, d, J=8.8Hz), 7.76 (1H, d, J=6.6Hz), 7.51-7.38 (5H, m), 7.21 (2H, m), 7.15-7.02 (2H, m), 3.89 (2H, d, J=5.6Hz), 3.80 (1H, t, J=7.6Hz), 2.13-1.99 and 1.84-1.69 (each 1H, m), 0.88 (3H, t, J=7.6Hz);

TLC : Rf 0.18 (chloroform:methanol:water=8:2:0.2).

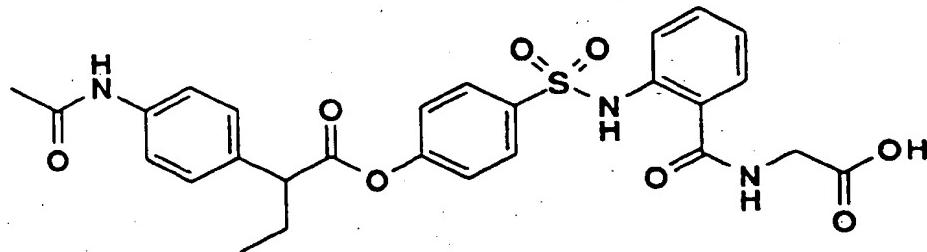
Example 2(225)

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4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(N-acetylarnino)phenyl)butanoic acid ester

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EP 0 769 498 A1

NMR (DMSO-d₆): δ 12.76 (1H, br), 11.58 (1H, s), 9.94 (1H, s), 9.20 (1H, t, J=6Hz), 7.81-7.70 (3H, m), 7.58-7.46 (4H, m), 7.29-7.10 (5H, m), 3.89 (2H, d, J=6Hz), 3.76 (1H, t, J=7Hz), 2.14-1.99 and 1.83-1.69 (each 1H, m), 2.03 (3H, s), 0.87 (3H, t, J=7Hz);

TLC : Rf 0.20 (chloroform:methanol:water=8:2:0.2).

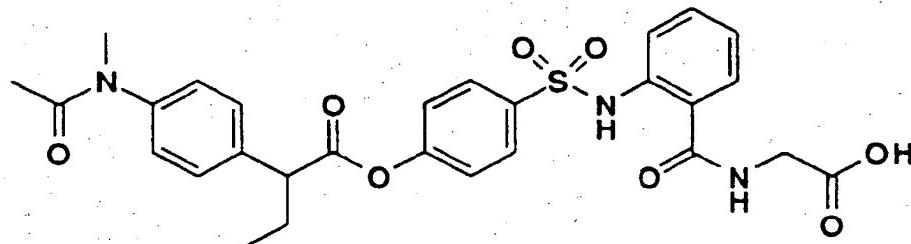
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Example 2(226)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(N-methyl-N-acetylaminophenyl)butanoic acid ester

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NMR (DMSO-d₆): δ 11.59 (1H, s), 9.19 (1H, t, J=5Hz), 7.80 (2H, d, J=9Hz), 7.73 (1H, d, J=8Hz), 7.53-7.41 (4H, m), 7.34-7.10 (5H, m), 3.89 (2H, d, J=6Hz), 3.69 (1H, t, J=7Hz), 3.16 (3H, s), 2.18-2.01 and 1.92-1.71 (each 1H, m), 1.78 (3H, s), 0.90 (3H, t, J=7Hz);

25

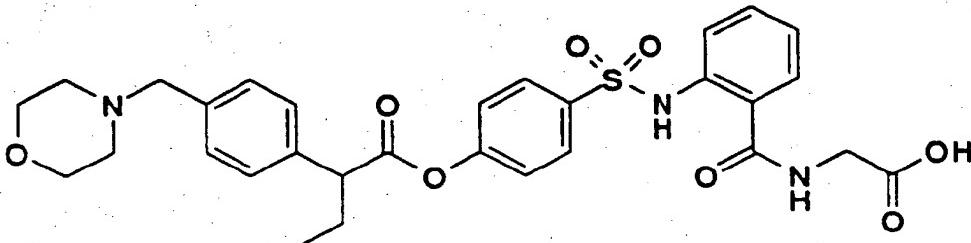
TLC : Rf 0.27 (chloroform:methanol:water=8:2:0.2).

Example 2(227)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(morpholin-4-ylmethyl)phenyl)butanoic acid ester · trifluoroacetate

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· CF₃COOH

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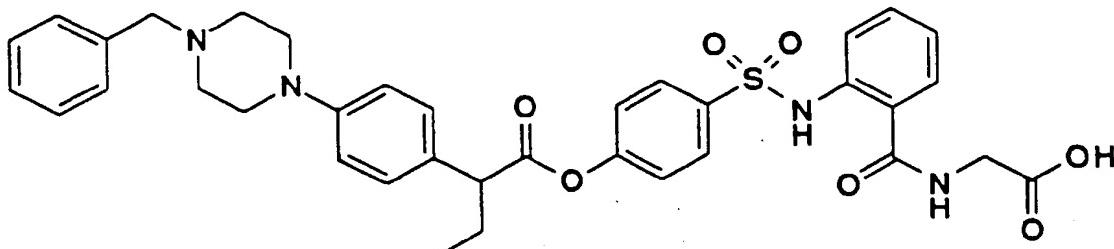
NMR (DMSO-d₆): δ 12.00-11.20 (2H, br), 9.28-9.15 (1H, m), 7.88-7.68 (3H, m), 7.56-7.27 (6H, m), 7.27-7.08 (3H, m), 3.95-3.79 (4H, m), 3.68-3.59 (5H, m); 2.90-2.60 (4H, m), 2.20-1.95 (1H, m), 1.95-1.65 (1H, m), 0.95-0.80 (3H, m); TLC : Rf 0.47 (acetic acid:methanol:chloroform=1:2:20).

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Example 2(228)

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(4-benzylpiperazin-1-yl)phenyl)butanoic acid ester

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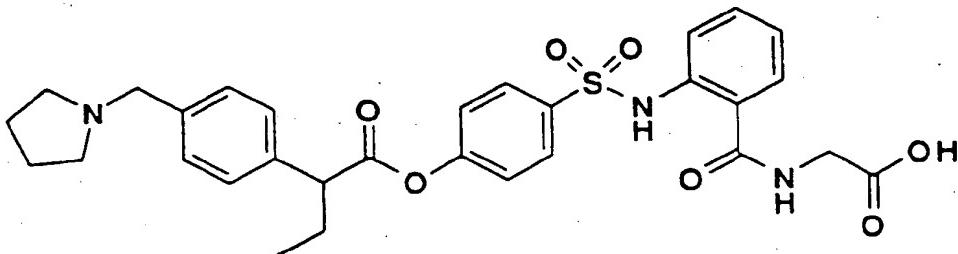


15 NMR ($\text{CDCl}_3+\text{CD}_3\text{OD}$): δ 9.21 (1H, d-like), 7.95-7.86 (4H, m), 7.78-7.71 (1H, m), 7.65-7.58 (2H, m), 7.54-7.46 (6H, m), 7.40-7.32 (2H, m), 7.21-7.10 (2H, m), 3.91 (2H, d, $J=7\text{Hz}$), 3.50-3.06 (11H, m), 1.68-1.45 (2H, m), 0.78 (3H, t, $J=7\text{Hz}$);

15 TLC : Rf 0.65 (acetic acid:methanol:chloroform=1:3:30).

Example 2(229)

20 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-ylmethyl)phenyl)butanoic acid
ester

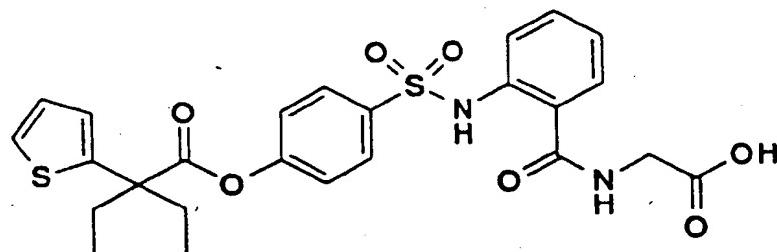


35 NMR (DMSO-d_6): δ 9.65 (1H, brs), 7.77 (2H, d, $J=8\text{Hz}$), 7.73 (1H, d, $J=8\text{Hz}$), 7.45-7.30 (6H, m), 7.14 (2H, d, $J=8\text{Hz}$), 6.99 (1H, d, $J=8\text{Hz}$), 4.03-3.93 (2H, m), 3.93-3.80 (3H, m), 2.88 (4H, brs), 2.09 (1H, ddq, $J=14\text{Hz}, 7\text{Hz}, 7\text{Hz}$), 1.88-1.73 (5H, m), 0.88 (3H, t, $J=7\text{Hz}$);

TLC : Rf 0.10 (acetic acid:methanol:chloroform=1:2:20).

Example 2(230)

40 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(thiophen-2-yl)-2-ethylbutanoic acid ester



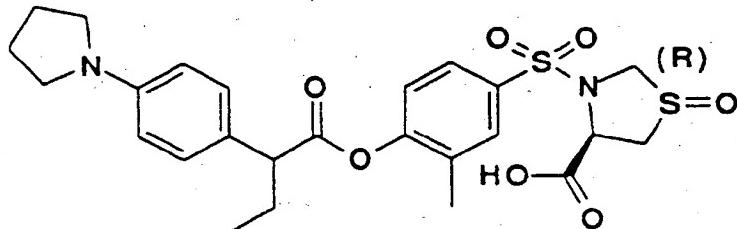
55 NMR (DMSO-d_6): δ 9.5-9.3 (1H, brs), 7.9-7.7 (3H, m), 7.5-7.4 (3H, m), 7.3-7.0 (5H, m), 3.87 (2H, d, $J=5\text{Hz}$), 2.3-1.9 (4H, m), 0.82 (6H, t, $J=7\text{Hz}$);
TLC : Rf 0.19 (acetic acid:methanol:chloroform=1:2:40).

Example 2(231)

4-((1R-oxo-4S-carboxyperhydrothiazol-3-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR (DMSO-d₆): δ 7.85-7.70 (2H, m), 7.18 (2H, d, J=8.5Hz), 7.09 (1H, d, J=8.5Hz), 6.53 (2H, d, J=8.5Hz), 4.85-4.65 (2H, m), 4.30 (1H, d, J=12.5Hz), 3.69 (1H, t, J=7.5Hz), 3.35-3.05 (6H, m), 2.20-1.60 (2H, m), 1.99 (3H, s), 2.00-1.85 (4H, m), 0.90 (3H, t, J=7.5Hz);

TLC : Rf 0.36 (chloroform:methanol:acetic acid=25:5:1).

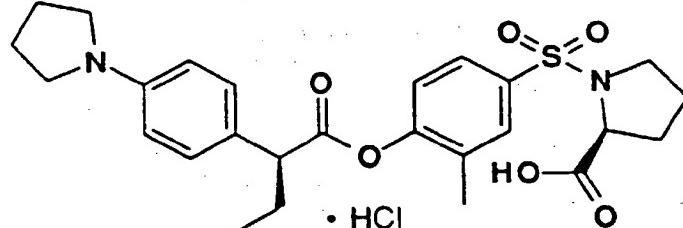
Example 2(232)

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4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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NMR (CD₃OD): δ 7.89-7.69 (2H, m), 7.54 and 7.41 (each 2H, d, J=8Hz), 7.15 (1H, d, J=8Hz), 4.28-4.16 (1H, m), 3.90 (1H, t, J=7Hz), 3.69-3.64 (4H, m), 3.51-3.40 and 3.31-3.21 (each 1H, m), 2.28-2.21 (5H, m), 2.02 (3H, s), 2.01-1.89 (4H, m), 1.80-1.65 (1H, m), 0.99 (3H, t, J=7Hz);

TLC : Rf 0.17 (chloroform:methanol:water=9:1:0.1).

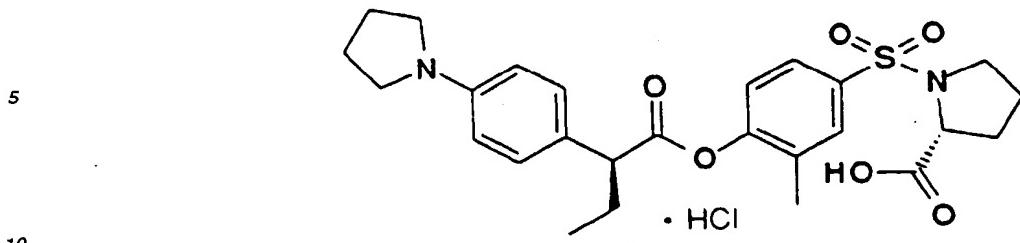
45

Example 2(233)

4-((2R-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

50

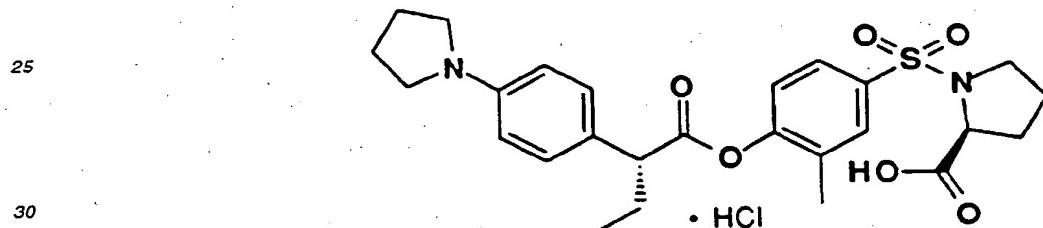
55



NMR (CD_3OD): δ 7.81-7.68 (2H, m), 7.56 and 7.45 (each 2H, d, $J=8\text{Hz}$), 7.15 (1H, d, $J=8\text{Hz}$), 4.28-4.16 (1H, m),
3.91 (1H, t, $J=7\text{Hz}$), 3.71-3.64 (4H, m), 3.50-3.40 and 3.33-3.22 (each 1H, m), 2.31-2.22 (5H, m), 2.03 (3H, s), 2.02-1.84
(4H, m), 1.80-1.64 (1H, m), 1.00 (3H, t, $J=7\text{Hz}$);
15 TLC : Rf 0.18 (chloroform:methanol:water=9:1:0.1).

Example 2(234)

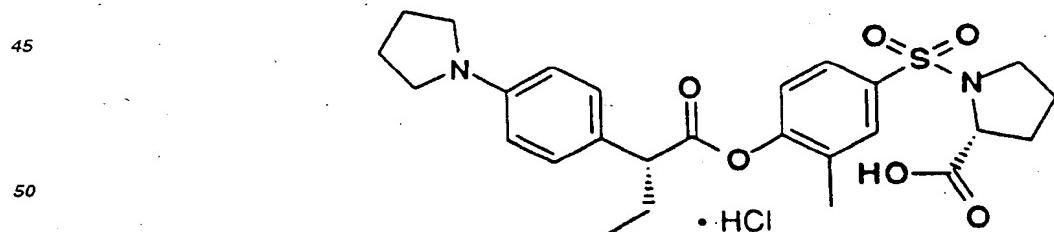
20 4-((2S-carboxypyrrrolidin-1-yl)sulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



NMR (CD_3OD): δ 7.80-7.68 (2H, m), 7.50 and 7.31 (each 2H, d, $J=8\text{Hz}$), 7.14 (1H, d, $J=8\text{Hz}$), 4.22-4.16 (1H, m),
3.87 (1H, t, $J=7\text{Hz}$), 3.68-3.56 (4H, m), 3.50-3.42 and 3.35-3.20 (each 1H, m), 2.32-2.18 (5H, m), 2.02 (3H, s), 2.01-1.83
(4H, m), 1.79-1.65 (1H, m), 0.99 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.17 (chloroform:methanol:water=9:1:0.1).

Example 2(235)

40 4-((2R-carboxypyrrrolidin-1-yl)sulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



55 NMR (CD_3OD): δ 7.77-7.68 (2H, m), 7.57 and 7.48 (each 2H, d, $J=8\text{Hz}$), 7.15 (1H, d, $J=8\text{Hz}$), 4.22-4.17 (1H, m),
3.93 (1H, t, $J=7\text{Hz}$), 3.74-3.66 (4H, m), 3.52-3.42 and 3.35-3.21 (each 1H, m), 2.28-2.22 (5H, m), 2.02 (3H, s), 2.01-1.87
(4H, m), 1.80-1.64 (1H, m), 0.99 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.18 (chloroform:methanol:water=9:1:0.1).

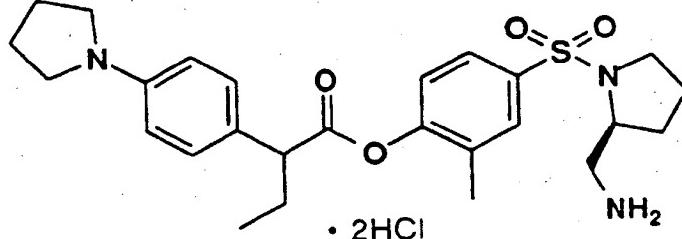
Example 2(236)

4-((2S-aminomethylpyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
2hydrochloride

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NMR (CD_3OD): δ 7.85-7.70 (2H, m), 7.64 (4H, s), 7.22 (1H, d, $J=8.0\text{Hz}$), 3.98 (1H, t, $J=8.0\text{Hz}$), 4.00-3.80 (1H, m), 3.85-3.70 (4H, m), 3.55-3.20 (2H, m), 3.15-2.95 (2H, m), 2.40-1.80 (2H, m), 2.35-2.25 (4H, m), 2.06 (3H, s), 2.00-1.40 (4H, m), 1.00 (3H, t, $J=7.5\text{Hz}$);

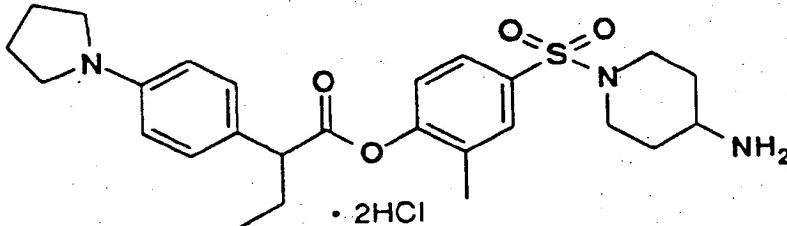
TLC : Rf 0.29 (chloroform:methanol:water=4:1:0.1).

Example 2(237)

25 4-((4-aminopiperidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
2hydrochloride

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NMR (DMSO-d_6): δ 8.14 (2H, brs), 7.63 (1H, s), 7.60 (1H, d, $J=8.4\text{Hz}$), 7.21 (2H, d, $J=8.4\text{Hz}$), 7.20 (1H, d, $J=8.4\text{Hz}$), 6.64 (2H, d, $J=8.4\text{Hz}$), 3.8-3.5 (4H, br), 3.3-3.2 (5H, br), 3.2-3.0 (1H, br), 2.5-2.3 (2H, m), 2.2-2.0 (1H, m), 2.0-1.9 (4H, br), 1.98 (3H, s), 1.9-1.7 (1H, m), 1.7-1.5 (2H, m), 0.90 (3H, t, $J=7.2\text{Hz}$);

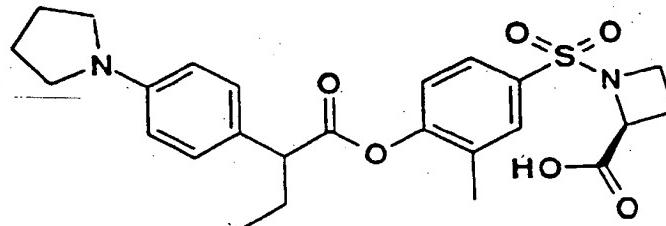
TLC : Rf 0.20 (chloroform:methanol=9:1).

Example 2(238)

45 4-((2S-carboxyazetidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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EP 0 769 498 A1

NMR (CD_3OD): δ 7.72 (1H, s), 7.71 (1H, d, $J=8.0\text{Hz}$), 7.22 (2H, d, $J=8.8\text{Hz}$), 7.17 (1H, d, $J=8.0\text{Hz}$), 6.58 (2H, d, $J=8.8\text{Hz}$), 4.30 (1H, t, $J=8.5\text{Hz}$), 3.8-3.6 (3H, m), 3.4-3.2 (4H, m), 2.4-2.1 (3H, m), 2.1-2.0 (4H, brs), 2.0-1.8 (1H, m), 2.04 (3H, s), 1.00 (3H, t, $J=7.4\text{Hz}$);

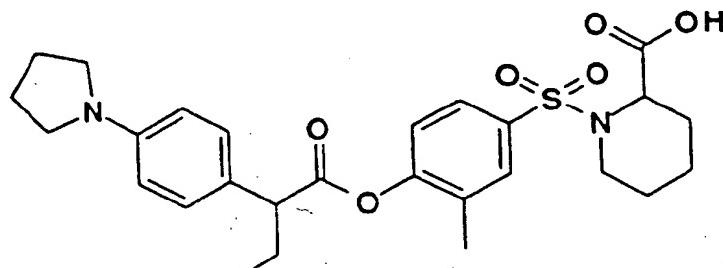
TLC : Rf 0.59 (chloroform:methanol:acetic acid=25:5:1).

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Example 2(239)

4-((2RS-carboxypiperidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR (CDCl_3): δ 7.65 (1H, s), 7.63 (1H, d, $J=8.2\text{Hz}$), 7.21 (2H, d, $J=8.6\text{Hz}$), 6.99 (1H, d, $J=8.2\text{Hz}$), 6.53 (2H, d, $J=8.6\text{Hz}$), 4.7-4.6 (1H, brs), 4.7-4.1 (1H, br), 3.59 (1H, t, $J=7.7\text{Hz}$), 3.5-3.2 (6H, brs), 2.3-2.1 (1H, m), 2.1-1.9 (4H, brs), 2.0-1.8 (1H, m), 1.98 (3H, s), 1.6-1.2 (6H, br), 0.96 (3H, t, $J=7.4\text{Hz}$);

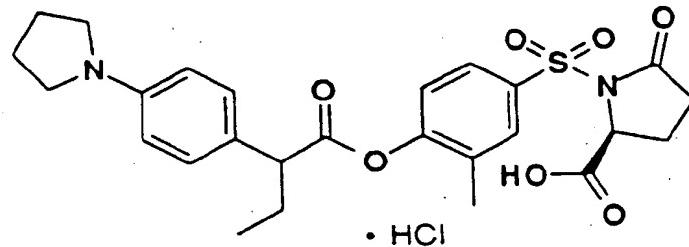
TLC : Rf 0.12 (chloroform:methanol=9:1).

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Example 2(240)

4-((2-oxo-5S-carboxypyrrrolidin-1-yl)sulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester hydrochloride

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NMR (CD_3OD): δ 7.96-7.82 (2H, m), 7.57 (2H, d, $J=8.5\text{Hz}$), 7.42 (2H, d, $J=8.5\text{Hz}$), 7.13 (1H, d, $J=8.0\text{Hz}$), 4.90-4.80 (1H, m), 3.92 (1H, t, $J=7.5\text{Hz}$), 3.74-3.60 (4H, m), 2.65-1.80 (10H, m), 2.02 (3H, s), 0.99 (3H, t, $J=7.5\text{Hz}$);

TLC : Rf 0.35 (chloroform:methanol:acetic acid=4:1:0.1).

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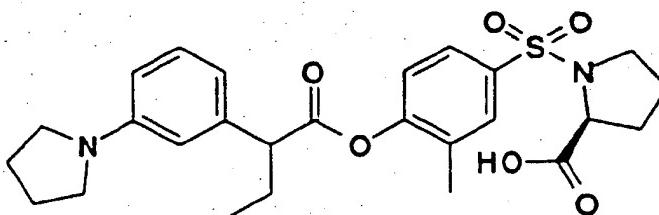
Example 2(241)

4-((2S-carboxypyrrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(3-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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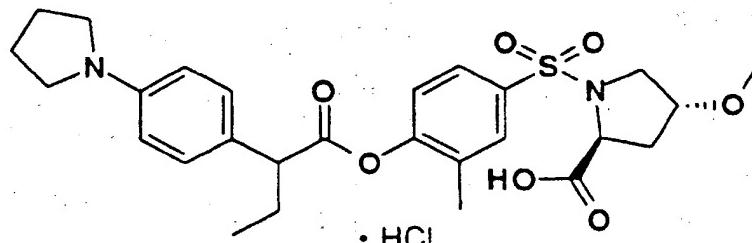
55



NMR (CDCl_3): δ 7.70-7.64 (2H, m), 7.20 (1H, t, $J=7.8\text{Hz}$), 7.09 (1H, d, $J=7.8\text{Hz}$), 6.66 (1H, d, $J=7.8\text{Hz}$), 6.53-6.47 (2H, m), 4.3-4.2 (1H, m), 3.8-3.4 (2H, m), 3.4-3.2 (5H, m), 2.3-1.7 (13H, m), 1.01 (3H, t, $J=7.4\text{Hz}$);
TLC: R_f 0.58 (chloroform:methanol:acetic acid=9:1:0.2).

Example 2(242)

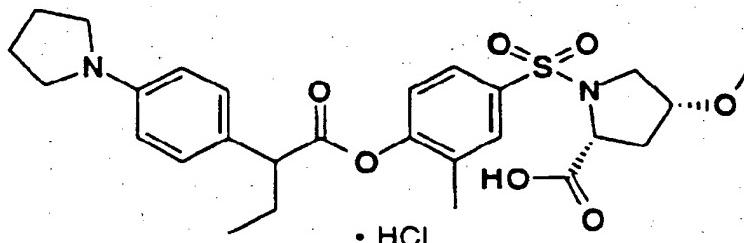
4-((2S-carboxy-4R-methoxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



NMR (DMSO-d₆): δ 7.73 (1H, s), 7.66 (1H, d, J=8.6Hz), 7.26 (2H, d, J=8.8Hz), 7.15 (1H, d, J=8.6Hz), 6.78 (2H, d, J=8.8Hz), 5.00 (1H, brs), 4.02 (1H, t, J=7Hz), 3.82 (1H, m), 3.76 (1H, t, J=7Hz), 3.41 (2H, m), 3.31 (4H, m), 2.83 (3H, s), 2.15 (2H, m), 2.00 (4H, m), 1.98 (3H, s), 1.95 (2H, m), 0.92 (3H, t, J=7.4Hz);
TLC : Rf 0.34 (chloroform:methanol:water=4:1:0.1)

Example 2(243)

40 4-((2R-carboxy-4R-methoxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid
ester · hydrochloride



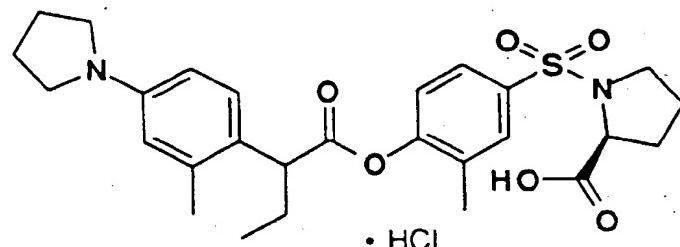
55 NMR (DMSO- d_6): δ 7.77 (1H, d, $J=2.4\text{Hz}$), 7.70 (1H, dd, $J=8.4\text{Hz}, 2.4\text{Hz}$), 7.26 (2H, d, $J=8.2\text{Hz}$), 7.16 (1H, d, $J=8.4\text{Hz}$), 6.75 (2H, d, $J=8.2\text{Hz}$), 4.80 (1H, brs), 4.31 (1H, dd, $J=9.2\text{Hz}, 3.2\text{Hz}$), 3.76 (2H, m), 3.33 (6H, m), 3.12 (3H, s), 2.12 (2H, m), 2.02 (4H, m), 1.98 (3H, s), 1.80 (2H, m), 0.91 (3H, t, $J=7.2\text{Hz}$);
TLC : Rf 0.47 (chloroform:methanol:water=4:1:0.1)

Example 2(244)

4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(2-methyl-4-(pyrrolidin-1-yl)phenyl)butanoic acid · ester hydrochloride

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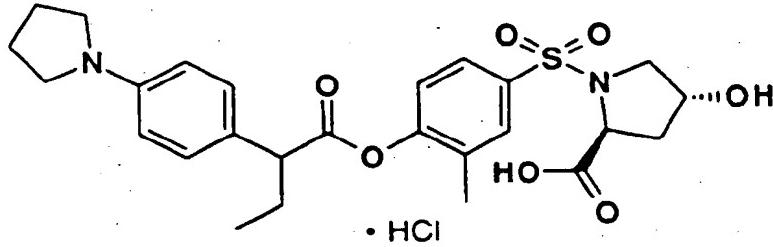
NMR (CD_3OD): δ 7.76-7.66 (2H, m), 7.60-7.40 (3H, m), 7.15 (1H, d, $J=8.0\text{Hz}$), 4.30-4.10 (2H, m), 3.85-3.70 (4H, m), 3.55-3.15 (2H, m), 2.57 (3H, s), 2.40-2.15 (5H, m), 2.00 (3H, s), 2.10-1.60 (5H, m), 1.01 (3H, t, $J=7.5\text{Hz}$);
TLC : Rf 0.33 (chloroform:methanol:acetic acid=4:1:0.1).

Example 2(245)

4-((2S-carboxy-4R-hydroxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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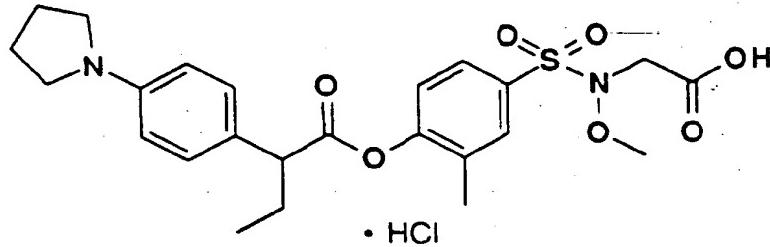
NMR (CD_3OD): δ 7.72 (1H, s), 7.70 (1H, m), 7.20 (2H, d, $J=8.6\text{Hz}$), 7.09 (1H, d, $J=8.0\text{Hz}$), 6.58 (2H, d, $J=8.6\text{Hz}$), 4.32 (1H, m), 4.21 (1H, m), 3.73-3.42 (2H, m), 3.38-3.16 (5H, m), 2.35-1.68 (11H, m), 0.98 (3H, t, $J=7.0\text{Hz}$);
TLC : Rf 0.55 (chloroform:methanol:acetic acid=15:2:1).

Example 2(246)

4-(N-methoxy-N-carboxymethylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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EP 0 769 498 A1

NMR (CDCl_3): δ 7.66 (1H, s), 7.63 (1H, d, $J=8.0\text{Hz}$), 7.22 (2H, d, $J=8.8\text{Hz}$), 7.08 (1H, d, $J=8.0\text{Hz}$), 6.54 (2H, d, $J=8.8\text{Hz}$), 5.3-4.6 (1H, br), 3.81 (3H, s), 3.70 (2H, s), 3.69 (1H, t, $J=7.8\text{Hz}$), 3.3-3.2 (4H, brs), 2.2-2.0 (1H, m), 2.1-1.9 (4H, brs), 2.01 (3H, s), 2.0-1.8 (1H, m), 0.97 (3H, t, $J=7.4\text{Hz}$);
 TLC : Rf 0.44 (hexane:ethyl acetate=2:1).

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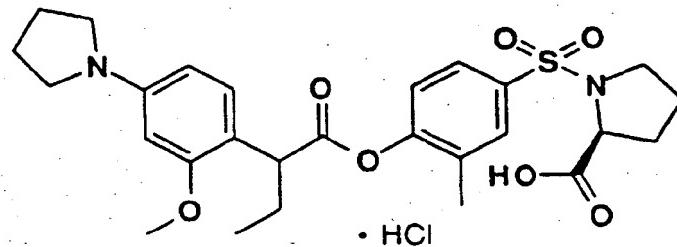
Example 2(247)

4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(2-methoxy-4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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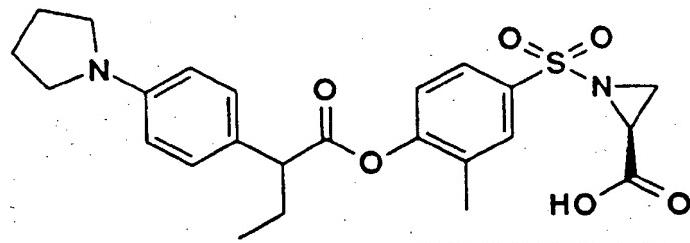
Example 2(248)

4-((2S-carboxyaziridin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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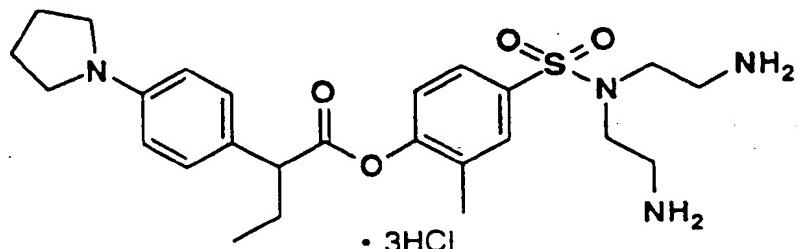


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Example 2(249)

4-(N,N-bis(2-aminoethyl)aminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 3hydrochloride

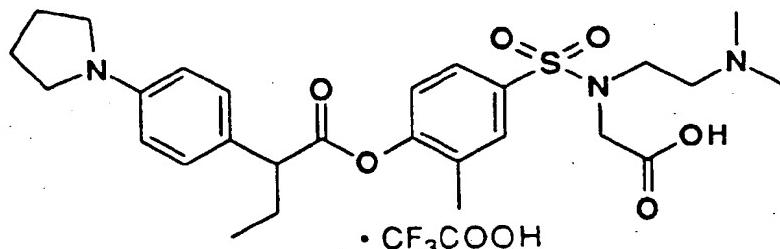
55



15 NMR (DMSO-d₆): δ 8.25 (4H, m), 7.80 (1H, d, J=1.0Hz), 7.71 (1H, dd, J=8.6Hz, 1.0Hz), 7.26 (3H, m), 6.82 (2H, m), 3.78 (1H, t, J=7.8Hz), 3.35 (8H, m), 3.04 (4H, m), 2.13 (1H, m), 2.02 (3H, s), 1.98 (4H, m), 1.85 (1H, m), 0.92 (3H, t, J=7.2Hz);
TLC : Rf 0.31 (chloroform:methanol:water=6:4:1).

Example 2(250)

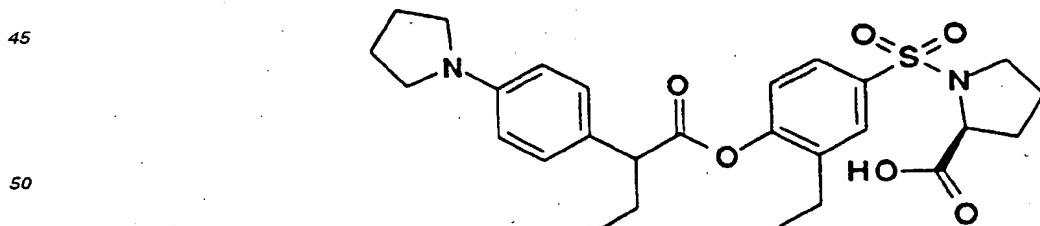
20 4-(N-carboxymethyl-N-(2-(N',N'-dimethylamino)ethyl)aminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester - trifluoroacetate



35 NMR (CDCl₃): δ 7.61-7.55 (2H, m), 7.21 (2H, d, J=8.7Hz), 7.07 (1H, d, J=8.2Hz), 6.54 (2H, d, J=8.7Hz), 3.80 (2H, s), 3.60 (1H, t, J=7.8Hz), 3.55-3.10 (8H, m), 2.83 (6H, s), 2.30-1.70 (9H, m), 0.98 (3H, t, J=7.4Hz);
TLC : Rf 0.43 (chloroform:methanol:water=8:2:0.2).

Example 2(251)

40 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-ethylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



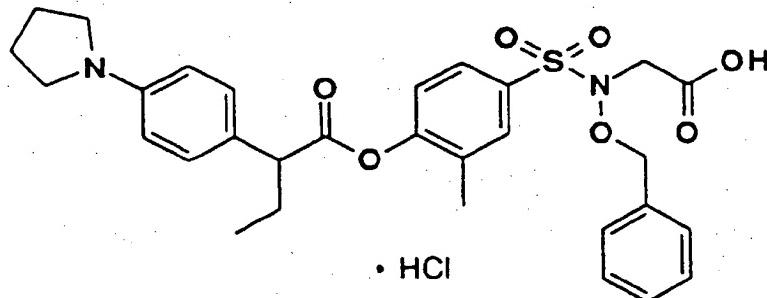
55 NMR (CDCl₃): δ 7.8-7.6 (m, 2H), 7.36 (d, J=8.4Hz, 2H), 7.07 (d, J=8.4Hz, 1H), 7.02 (d, J=8.4Hz, 2H), 4.3-4.2 (m, 1H), 3.70 (t, J=7.2Hz, 1H), 3.6-3.4 (m, 5H), 3.3-3.1 (m, 1H), 2.37 (q, J=7.6Hz, 2H), 2.3-1.6 (m, 10H), 1.03 (t, J=7.6Hz, 3H), 0.99 (t, J=7.6Hz, 3H);
TLC : Rf 0.33 (chloroform:methanol:acetic acid=50:2:1).

Example 2(252)

4-(N-carboxymethyl-N-benzyloxyaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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NMR (DMSO-d₆): δ 7.70 (1H, s), 7.68 (1H, d, J=8.6Hz), 7.32 (5H, s), 7.20 (2H, d, J=8.2Hz), 7.16 (1H, d, J=8.6Hz), 6.52 (2H, d, J=8.2Hz), 5.25 (2H, s), 3.8-3.4 (2H, m), 3.5-3.4 (2H, brs), 3.3-3.1 (4H, brs), 2.2-2.0 (1H, m), 2.0-1.8 (4H, brs), 1.9-1.7 (1H, m), 1.93(3H, s), 0.89 (3H, t, J=7.2Hz);
TLC : Rf 0.29 (chloroform:methanol=9:1).

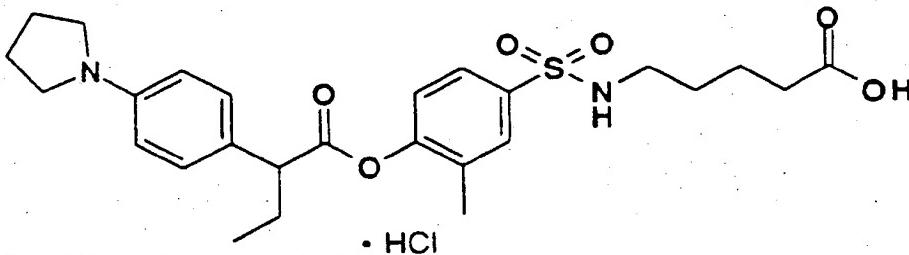
25

Example 2(253)

4-(N-(4-carboxybutyl)aminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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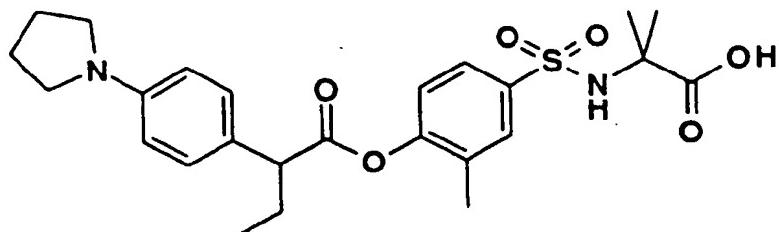
45

NMR (DMSO-d₆ + 2 drops of D₂O): δ 7.66 (1H, s-like), 7.63 (1H, dd, J=2 and 8Hz), 7.24 (2H, d, J=8Hz), 7.14 (2H, d, J=8Hz), 6.69 (2H, d, J=8Hz), 3.74 (1H, t, J=7Hz), 3.31-3.25 (4H, m), 2.71 (2H, t, J=7Hz), 2.18-1.72 (2H, m), 2.15 (2H, t, J=7Hz), 2.01-1.94 (4H, m), 1.96 (3H, s), 1.53-1.34 (4H, m), 0.91 (3H, t, J=7Hz);
TLC : Rf 0.38 (chloroform:methanol:water=9:1:0.1).

Example 2(254)

50 4-(N-(1,1-dimethyl-1-carboxymethyl)aminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

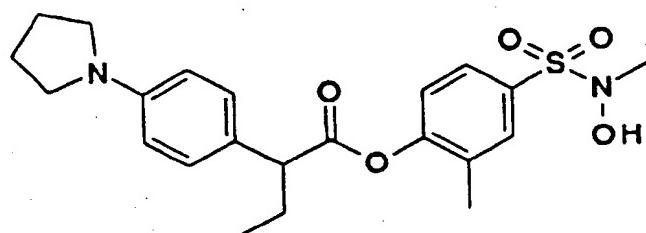
55



15 NMR (DMSO-d₆): δ 7.68 (1H, s-like), 7.64 (1H, dd, J=2 and 8Hz), 7.39 (1H, br), 7.18 (2H, d, J=8Hz), 7.07 (1H, d, J=8Hz), 6.53 (2H, d, J=8Hz), 3.69 (1H, t, J=7Hz), 3.24-3.18 (4H, m), 2.20-1.65 (2H, m), 1.98-1.91 (4H, m), 1.93 (3H, s) 1.18 (6H, s), 0.90 (3H, t, J=7Hz);
TLC : Rf 0.19 (chloroform:methanol:water=9:1:0.1).

Example 2(255)

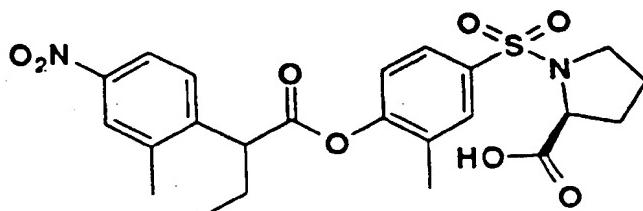
20 4-(N-methyl-N-hydroxyaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



35 NMR (CDCl₃): δ 7.71 (1H, s), 7.69 (1H, d, J=8.6Hz), 7.23 (2H, d, J=8.8Hz), 7.13 (1H, d, J=8.6Hz), 6.55 (2H, d, J=8.8Hz), 6.54 (1H, s), 3.63 (1H, t, J=7.7Hz), 3.3-3.2 (4H, brs), 2.81 (3H, s), 2.3-2.1 (1H, m), 2.1-1.9 (4H, brs), 2.06 (3H, s), 2.0-1.8 (1H, m), 0.99 (3H, t, J=7.3Hz);
TLC : Rf 0.43 (hexane:ethyl acetate=2:1).

Example 2(256)

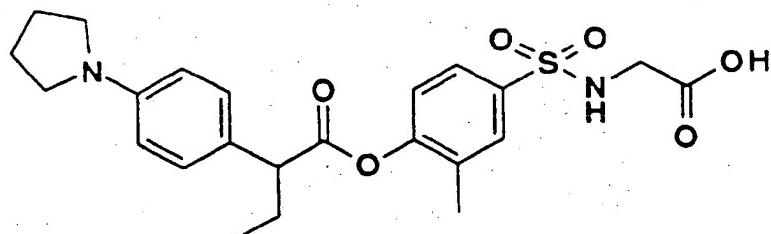
40 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(2-methyl-4-nitrophenyl)butanoic acid ester



55 NMR (CDCl₃): δ 8.15-8.05 (2H, m), 7.75-7.65 (2H, m), 7.56 (1H, d, J=8.0Hz), 7.09 (1H, d, J=9.0Hz), 4.25 (1H, dd, J=3.5, 7.0Hz), 4.13 (1H, t, J=7.5Hz), 3.60-3.40 (1H, m), 3.30-3.10 (1H, m), 2.59 (3H, s), 2.45-1.60 (6H, m), 1.99 (3H, s), 1.02 (3H, t, J=7.5Hz);
TLC : Rf 0.24 (chloroform:methanol:water=9:1:0.1).

Example 2(257)

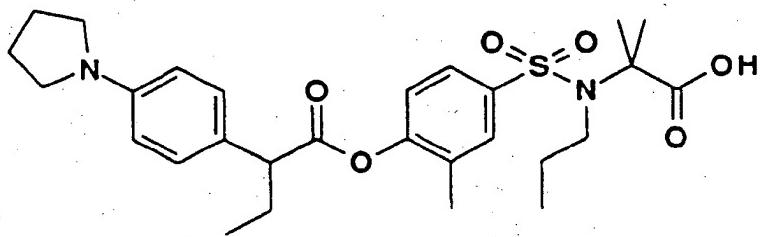
4-(N-carboxymethylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



NMR (CDCl_3): δ 7.70-7.58 (2H, m), 7.25 (2H, d, $J=8\text{Hz}$), 7.01 (1H, d, $J=8\text{Hz}$), 6.65 (2H, d, $J=8\text{Hz}$), 5.43-5.23 (1H, br), 5.18-4.80 (1H, br), 3.75 (2H, brs), 3.63 (1H, t, $J=7\text{Hz}$), 3.40-3.20 (4H, m), 2.28-1.80 (9H, m), 0.98 (3H, t, $J=7\text{Hz}$);
TLC : Rf 0.11 (chloroform:methanol:acetic acid=40:2:1).

Example 2(258)

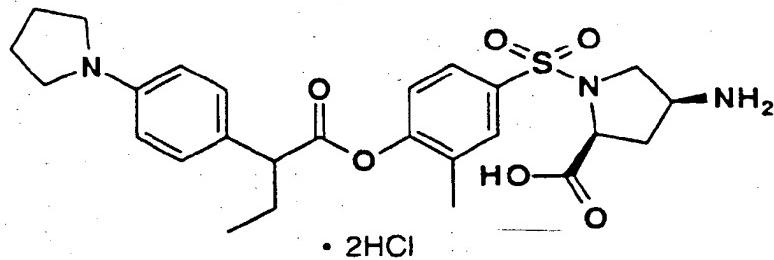
4-(N-(1,1-dimethyl-1-carboxymethyl)-N-propylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butoanoic acid ester



³⁵ NMR (DMSO-d₆ + 2 drops of D₂O): δ 7.80 (1H, s-like), 7.78 (1H, dd, J=2 and 8Hz), 7.18 (2H, d, J=8Hz), 7.11 (1H, d, J=8Hz), 6.54 (2H, d, J=8Hz), 3.70 (1H, t, J=7Hz), 3.25-3.17 (4H, m), 3.12-3.04 (2H, m), 2.20-1.70 (2H, m), 1.99-1.92 (4H, m), 1.95 (3H, s), 1.57-1.42 (2H, m), 1.45 (6H, s), 0.91 (3H, t, J=7Hz), 0.71 (3H, t, J=7Hz); TLC : Rf 0.57 (chloroform:methanol:water=9:1:0.1).

Example 2(259)

4-((2S-carboxy-4S-aminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride



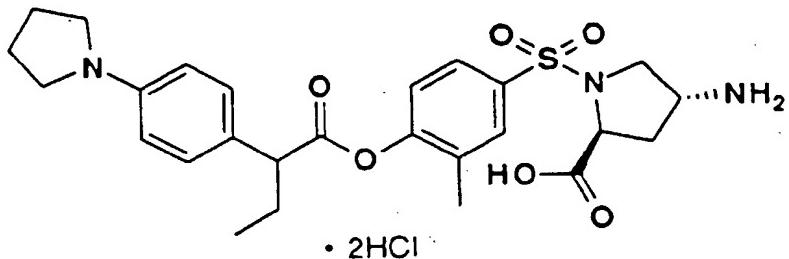
NMR (CD_3OD): δ 7.83-7.68 (2H, m), 7.63 (4H, s-like), 7.22 (1H, d, $J=8.2\text{Hz}$), 4.21 (1H, dd, $J=9.2$ and 3.4Hz), 3.98 (1H, t, $J=7.8\text{Hz}$), 3.90-3.43 (7H, m), 2.70-1.84 (8H, m), 2.06 (3H, s), 1.00 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.46 (ethyl acetate:acetic acid:water=6:2:1).

Example 2(260)

4-((2S-carboxy-4R-aminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

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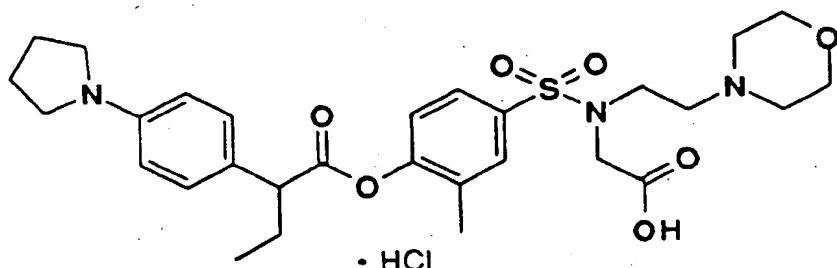
15

NMR (CD_3OD): δ 7.84-7.68 (2H, m), 7.63 (4H, s-like), 7.18 (1H, d, $J=8.0\text{Hz}$), 4.55 (1H, dd, $J=8.4$ and 4.2Hz),
4.07-3.90 (2H, m), 3.90-3.63 (5H, m), 3.47-3.26 (1H, m), 2.53-1.82 (8H, m), 2.05 (3H, s), 1.00 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.42 (ethyl acetate:acetic acid:water=6:2:1).

Example 2(261)

25 4-(N-carboxymethyl-N-(2-(morpholin-4-yl)ethyl)aminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

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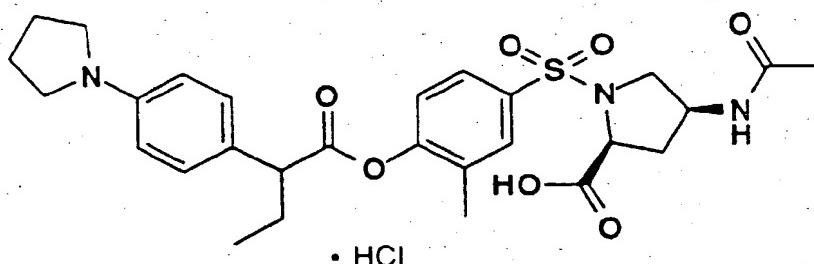
40 NMR (CDCl_3): δ 7.66-7.52 (2H, m), 7.21 (2H, d, $J=8.5\text{Hz}$), 7.09 (1H, d, $J=8.5\text{Hz}$), 6.55 (2H, d, $J=8.5\text{Hz}$), 3.95-3.80 (4H, m), 3.75 (2H, s), 3.61 (1H, t, $J=7.5\text{Hz}$), 3.45-3.20 (6H, m), 3.10-2.70 (6H, m), 2.30-1.75 (6H, m), 2.04 (3H, s), 0.99 (3H, t, $J=7.5\text{Hz}$);
TLC : Rf 0.24 (chloroform:methanol:water=9:1:0.1).

45 Example 2(262)

4-((2S-carboxy-4S-acetylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

50

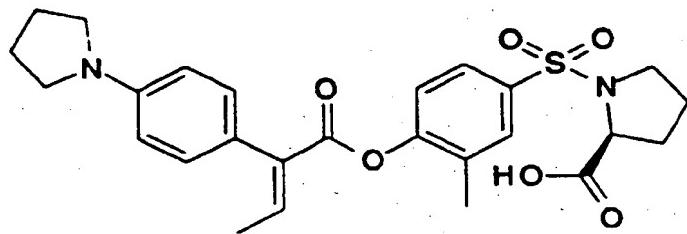
55



15 NMR (DMSO-d₆): δ 8.02 (1H, d, J=7.8Hz), 7.74 (1H, d, J=2.2Hz), 6.69 (1H, dd, J=8.4Hz, 2.2Hz), 7.17 (2H, d, J=6Hz), 7.17 (1H, d, J=8.4Hz), 6.54 (2H, d, J=8.6Hz), 4.13 (1H, t, J=7.8Hz), 3.82 (1H, m), 3.70 (1H, t, J=7.6Hz), 3.50 (1H, m), 3.22 (4H, m), 3.06 (1H, m), 2.31 (1H, m), 2.07 (1H, m), 1.99 (3H, s), 1.96 (4H, m), 1.82 (2H, m), 1.75 (3H, s), 0.91 (3H, t, J=7.4Hz);
TLC : Rf 0.18 (chloroform:methanol:water=4:1:0.1).

20 Example 2(263)

4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)-2-butenic acid ester

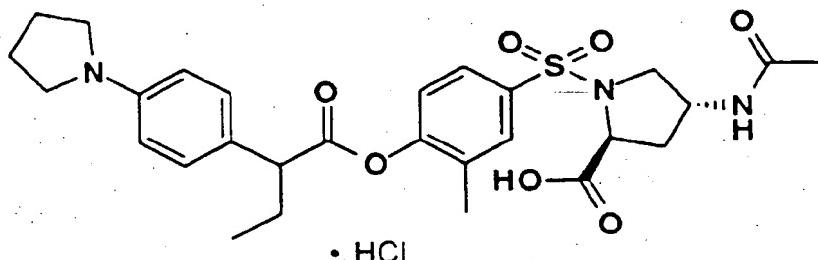


35 NMR (CDCl₃): δ 7.80-7.65 (2H, m), 7.32 (1H, q, J=7Hz), 7.23 (1H, d, J=8Hz), 7.13 (2H, d, J=8Hz), 6.59 (2H, d, J=8Hz), 4.30-4.20 (1H, m), 4.10-3.60 (1H, b), 3.60-3.45 (1H, m), 3.40-3.20 (5H, m), 2.30-1.65 (8H, m), 2.25 (3H, s), 1.88 (3H, d, J=7Hz);
TLC : Rf 0.28 (chloroform:methanol:acetic acid=4:2:0.1).

40 Example 2(264)

4-((2S-carboxy-4R-acetylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

45



EP 0 769 498 A1

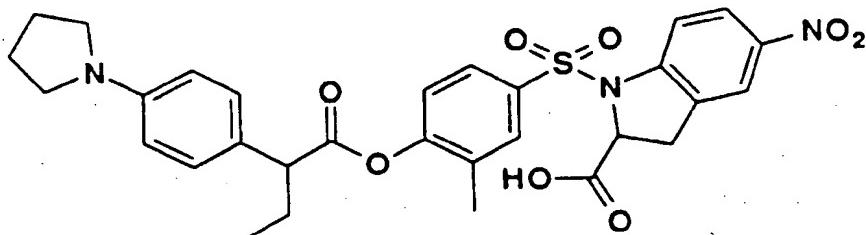
NMR (DMSO-d₆): δ 7.78 (1H, d, J=5Hz), 7.68 (1H, s), 7.64 (1H, d, J=8.0Hz), 7.19 (2H, d, J=8.6Hz), 7.16 (1H, d, J=8.0Hz), 6.56 (2H, d, J=8.6Hz), 4.28 (1H, t, J=7.8Hz), 4.12 (1H, m), 3.75 (1H, m), 3.48 (1H, m), 3.23 (4H, m), 3.06 (1H, m), 2.12 (1H, m), 2.03 (2H, m), 1.99 (3H, s), 1.96 (4H, m), 1.80 (1H, m), 1.54 (3H, s), 0.91 (3H, t, J=7.2Hz);
TLC : Rf 0.19 (chloroform:methanol:water=4:1:0.1).

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Example 2(265)

4-((2RS-carboxy-5-nitroindolin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

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NMR (CDCl₃): δ 8.33 (1H, d, J=2Hz), 7.89 (1H, dd, J=8, 2Hz), 7.67 (1H, s), 7.62 (1H, d, J=8Hz), 7.20 (1H, d, J=8Hz), 7.18 (2H, d, J=8Hz), 7.02 (1H, d, J=8Hz), 6.55 (2H, d, J=8Hz), 4.85 (1H, dd, J=10, 5Hz), 4.60-4.25 (1H, br), 3.59 (1H, t, J=7Hz), 3.40-3.15 (6H, m), 2.25-1.75 (9H, m), 0.95 (3H, t, J=7Hz);
TLC : Rf 0.30 (chloroform:methanol:acetic acid=4:2:0.1).

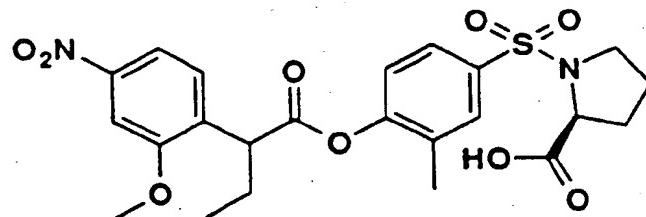
20

Example 2(266)

4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(2-methoxy-4-nitrophenyl)butanoic acid ester

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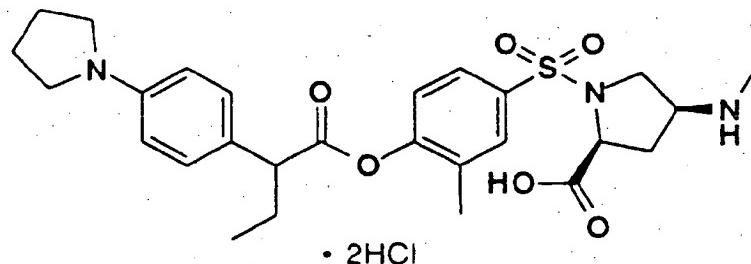
NMR (CDCl₃): δ 7.88 (1H, dd, J=2.0, 8.5Hz), 7.78 (1H, d, J=2.0Hz), 7.75-7.65 (2H, m), 7.49 (1H, d, J=8.5Hz), 7.12 (1H, d, J=9.0Hz), 4.30-4.15 (2H, m), 3.98 (3H, s), 3.60-3.40 (1H, m), 3.30-3.10 (1H, m), 2.40-1.60 (6H, m), 2.08 (3H, s), 1.00 (3H, t, J=7.5Hz);
TLC : Rf 0.38 (chloroform:methanol:acetic acid=4:2:0.1).

40

Example 2(267)

4-((2S-carboxy-4S-methylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

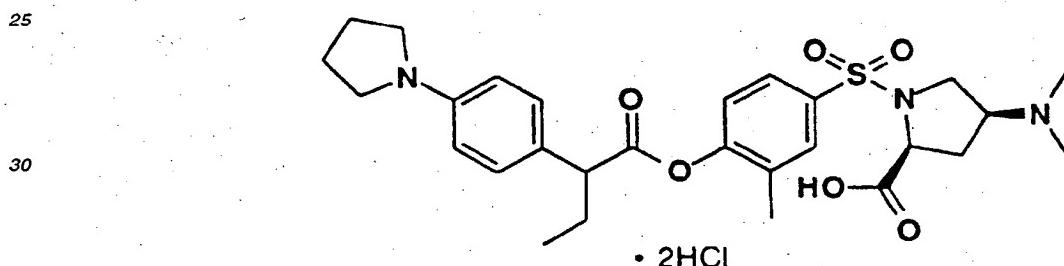
55



15 NMR (CD_3OD): δ 7.77 (1H, s), 7.75 (1H, d, $J=8.0\text{Hz}$), 7.37 (2H, d, $J=8.6\text{Hz}$), 7.19 (1H, d, $J=8.0\text{Hz}$), 6.98 (2H, d, $J=8.6\text{Hz}$), 4.18 (1H, m), 3.69 (3H, m), 3.59 (1H, m), 3.46 (4H, m), 2.72 (3H, s), 2.57 (1H, m), 2.21 (2H, m), 2.13 (4H, m), 2.02 (3H, s), 1.93 (1H, m), 0.98 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.28 (chloroform:methanol:water=4:1:0.1).

Example 2(268)

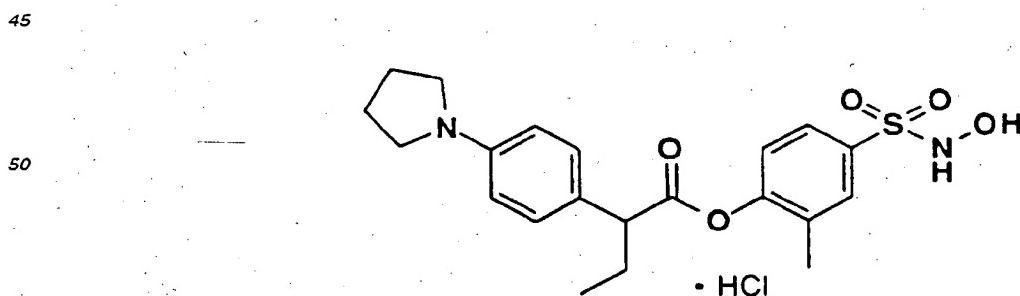
20 4-((2S-carboxy-4S-(N,N-dimethylamino)pyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester • 2hydrochloride



35 NMR (CD_3OD): δ 7.81 (1H, s), 7.78 (1H, d, $J=8.2\text{Hz}$), 7.62 (4H, s), 7.21 (1H, d, $J=8.2\text{Hz}$), 4.25 (1H, t, $J=7\text{Hz}$), 3.98 (1H, t, $J=7\text{Hz}$), 3.77 (4H, m), 3.65 (3H, m), 2.90 (6H, s), 2.80 (1H, m), 2.29 (4H, m), 2.24 (2H, m), 2.06 (3H, s), 1.99 (1H, m), 1.00 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.42 (chloroform:methanol:water=6:4:1).

Example 2(269)

40 4-(N-hydroxyaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester • hydrochloride



NMR (CDCl_3): δ 7.73 (1H, s), 7.68 (1H, d, $J=8.6\text{Hz}$), 7.23 (2H, d, $J=8.0\text{Hz}$), 7.2-7.0 (2H, br), 7.04 (1H, d, $J=8.6\text{Hz}$), 6.63 (2H, d, $J=8.0\text{Hz}$), 3.63 (1H, t, $J=7.7\text{Hz}$), 3.4-3.2 (4H, brs), 2.3-2.1 (1H, m), 2.1-1.9 (4H, brs), 2.00 (3H, s), 2.0-1.8

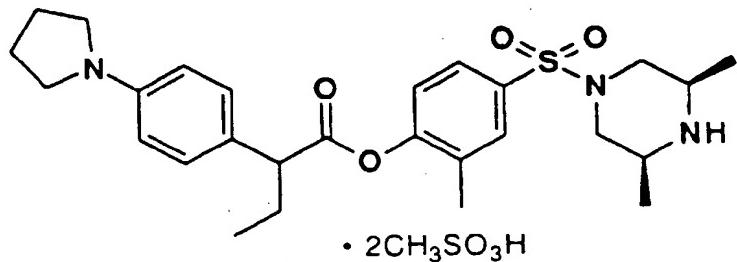
(1H, m), 0.97 (3H, t, J=7.3Hz);
TLC : Rf 0.25 (hexane:ethyl acetate=2:1).

Example 2(270)

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4-((2S,6S-dimethylpiperazin-4-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2methanesulfonic acid salt

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NMR (CDCl_3): 8.77-8.62 (6H, m), 7.23 (1H, d, $J=8.5\text{Hz}$), 4.01 (1H, t, $J=7.5\text{Hz}$), 4.00-3.75 (6H, m), 3.55-3.30 (2H, m), 2.68 (6H, s), 2.45-1.80 (8H, m), 2.07 (3H, s), 1.31 (6H, d, $J=6.5\text{Hz}$), 1.00 (3H, t, $J=7.5\text{Hz}$);
TLC : Rf 0.66 (chloroform:methanol:water=4:1:0.1).

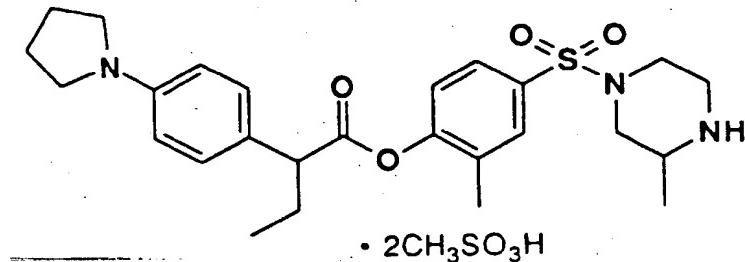
25

Example 2(271)

4-((2RS-methylpiperazin-4-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
2methanesulfonic acid salt

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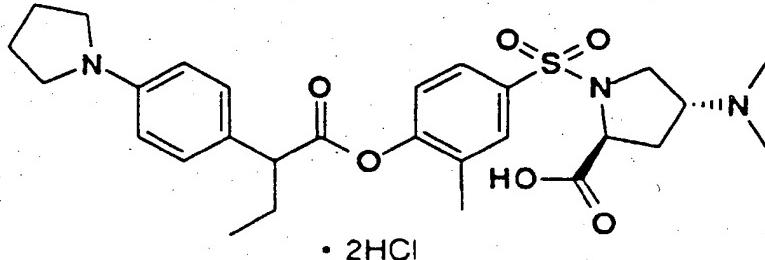
¹H NMR (CDCl_3): δ 7.76-7.60 (6H, m), 7.23 (1H, d, $J=8.0\text{Hz}$), 4.01 (1H, t, $J=7.5\text{Hz}$), 3.90-3.72 (6H, m), 3.55-3.35 (2H, m), 3.32-3.13 (1H, m), 2.82-2.62 (1H, m), 2.67 (6H, s), 2.49 (1H, dd, $J=13.0, 10.0\text{Hz}$), 2.40-1.80 (6H, m), 2.07 (3H, s), 1.32 (3H, d, $J=6.5\text{Hz}$), 1.00 (3H, t, $J=7.5\text{Hz}$);

45 TLC : Rf 0.45 (chloroform:methanol:water=9:1:0.1).

Example 2(272)

4-((2S-carboxy-4R-(N,N-dimethylamino)pyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

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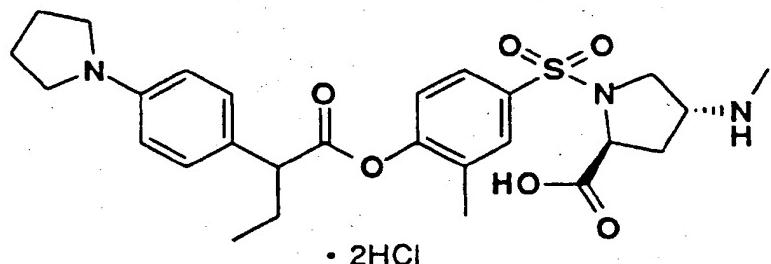


15 NMR (DMSO-d₆): δ 11.38 (1H, m), 7.77 (1H, s), 7.72 (1H, d, J=8.2Hz), 7.19 (3H, m), 6.63 (2H, d, J=8.6Hz), 4.38 (1H, m), 4.01 (1H, m), 3.82 (1H, m), 3.73 (1H, t, J=7.4Hz), 3.49 (1H, t, J=8.6Hz), 3.24 (4H, m), 2.70 (6H, s), 2.36 (2H, m), 2.11 (1H, m), 1.99 (3H, s), 1.97 (4H, m), 1.83 (1H, m), 0.91 (3H, t, J=7.2Hz);
TLC : R_f 0.44 (chloroform:methanol:water=6:4:1).

Example 2(273)

20 4-((2S-carboxy-4R-methylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester • 2hydrochloride

25

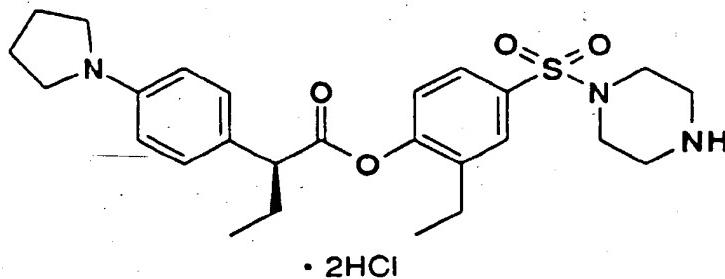


40 NMR (CD₃OD): δ 7.76 (1H, s), 7.73 (1H, d, J=8.0Hz), 7.25 (2H, d, J=8.4Hz), 7.13 (1H, d, J=8.0Hz), 6.71 (2H, d, J=8.4Hz), 4.53 (1H, m), 3.97 (1H, m), 3.86 (1H, m), 3.70 (1H, t, J=8Hz), 3.41 (1H, m), 3.35 (4H, m), 2.70 (3H, s), 2.49 (1H, m), 2.31 (1H, m), 2.17 (1H, m), 2.06 (4H, m), 2.00 (3H, s), 1.92 (1H, m), 0.98 (3H, t, J=7.2Hz);
TLC : R_f 0.46 (chloroform:methanol:water=6:4:1).

Example 2(274)

45 4-(piperazin-4-ylsulfonyl)-2-ethylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester • 2hydrochloride

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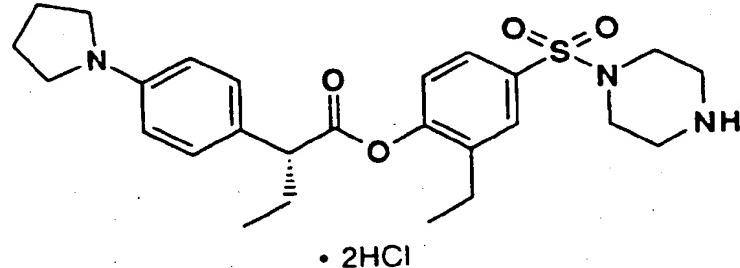
EP 0 769 498 A1

NMR (CD_3OD): δ 7.75-7.50 (6H, m), 7.25 (1H, d, $J=9.0\text{Hz}$), 3.97 (1H, t, $J=7.5\text{Hz}$), 3.85-3.70 (4H, m), 3.35-3.15 (8H, m), 2.50-1.80 (8H, m), 1.00 (6H, t, $J=7.5\text{Hz}$);
 TLC : Rf 0.46 (chloroform:methanol:water=9:1:0.1).

5 Example 2(275)

4-(piperazin-4-ylsulfonyl)-2-ethylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

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NMR (CD_3OD): δ 7.75-7.58 (6H, m), 7.25 (1H, d, $J=9.0\text{Hz}$), 3.98 (1H, t, $J=7.5\text{Hz}$), 3.90-3.70 (4H, m), 3.40-3.20 (8H, m), 2.50-1.80 (8H, m), 1.00 (6H, t, $J=7.5\text{Hz}$);
 TLC : Rf 0.46 (chloroform:methanol:water=9:1:0.1).

25

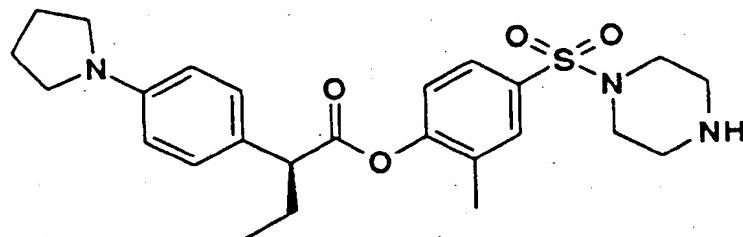
Example 2(276)

4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

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40



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NMR (CD_3OD): δ 7.71 (6H, m), 7.22 (1H, d, $J=8.0\text{Hz}$), 4.00 (1H, t, $J=8\text{Hz}$), 3.81 (4H, m), 3.31 (8H, s), 2.33 (4H, m), 2.24 (1H, m), 2.07 (3H, s), 1.98 (1H, m), 1.01 (3H, t, $J=7.4\text{Hz}$);

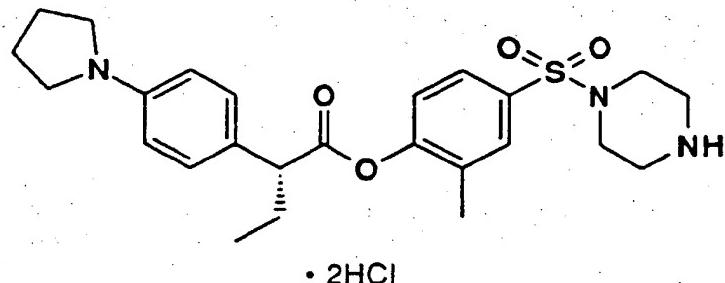
TLC : Rf 0.66 (chloroform:methanol:water=4:1:0.1).

50

Example 2(277)

— 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

55



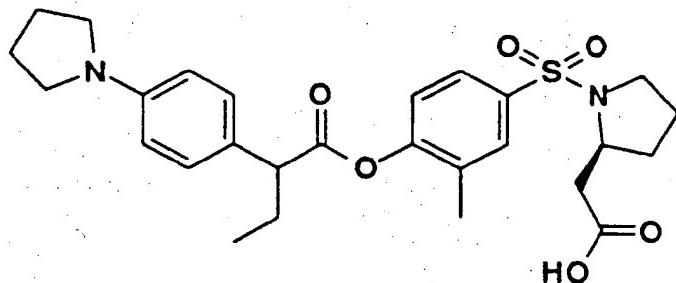
5

10

¹⁵ NMR (CD_3OD): δ 7.70 (6H, m), 7.22 (1H, d, $J=8.0\text{Hz}$), 4.00 (1H, t, $J=8\text{Hz}$), 3.81 (4H, m), 3.30 (8H, s), 2.32 (4H, m), 2.24 (1H, m), 2.06 (3H, s), 1.99 (1H, m), 1.00 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.66 (chloroform:methanol:water=4:1:0.1)

Example 2(278)

20 4-((2S-carboxymethylpyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



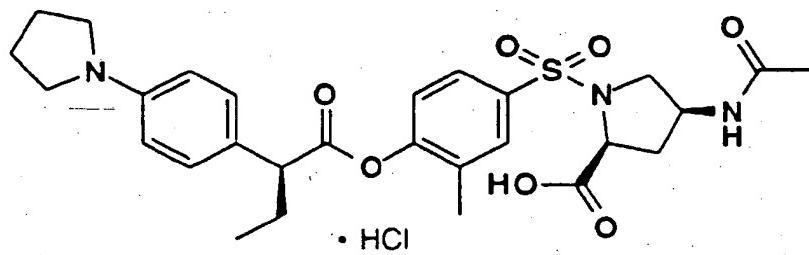
25

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35. NMR (CDCl_3): δ 7.70-7.58 (2H, m), 7.23 (2H, d, $J=8\text{Hz}$), 7.09 (1H, d, $J=8\text{Hz}$), 6.55 (2H, d, $J=8\text{Hz}$), 4.00-3.84 (1H, m), 3.62 (1H, t, $J=7\text{Hz}$), 3.50-3.35 (1H, m), 3.35-3.20 (4H, m), 3.18-3.03 (2H, m), 2.54 (1H, dd, $J=15, 10\text{Hz}$), 2.30-1.40 (13H, m), 0.98 (3H, t, $J=7\text{Hz}$);
TLC: Rf 0.39 (hexane:ethyl acetate:acetic acid=50:50:1).

40. Example 2(279)

4-((2S-carboxy-4-acetylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

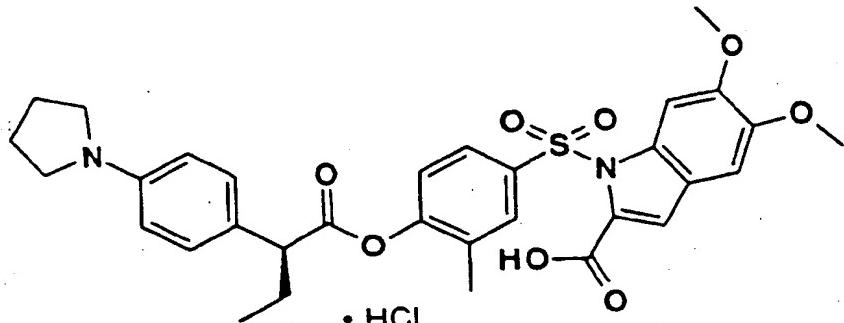


NMR (DMSO-d₆): δ 8.02 (1H, d, J=6Hz), 7.74 (1H, s), 7.69 (1H, d, J=8.8Hz), 7.24 (2H, d, J=8.6Hz), 7.18 (1H, d, J=8.6Hz), 6.69 (1H, d, J=8.8Hz), 4.15 (1H, t, J=7Hz), 3.75 (2H, ml, 3.51 (1H, m), 3.28 (4H, ml, 3.05 (1H, m), 2.33 (1H, m), 2.12 (1H, m), 1.99 (7H, s-like), 1.83 (2H, m), 1.75 (3H, s), 0.91 (3H, t, J=7.4Hz);

TLC : Rf 0.67 (chloroform:methanol:water=6:4:1).

Example 2(280)

5 4-((2-carboxy-5,6-dimethoxyindol-1-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
hydrochloride

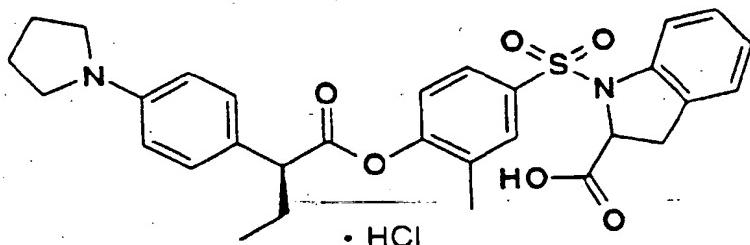


10 NMR (DMSO-d₆): δ 7.87 (1H, d, J=2.2Hz), 7.79 (1H, dd, J=8.6Hz, 2.2Hz), 7.50 (1H, s), 7.25-7.13 (5H, m), 6.66
15 (2H, d, J=8.0Hz), 3.88 (3H, s), 3.78 (3H, s), 3.71 (1H, t, J=7.2Hz), 3.26 (4H, m), 2.08 (1H, m), 1.97 (4H, m), 1.93 (3H,
s), 1.78 (1H, m), 0.88 (3H, t, J=7.6Hz);

20 TLC : Rf 0.45 (chloroform:methanol:water=4:1:0.1).

Example 2(281)

25 4-((2RS-carboxyindolin-1-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydro-
chloride

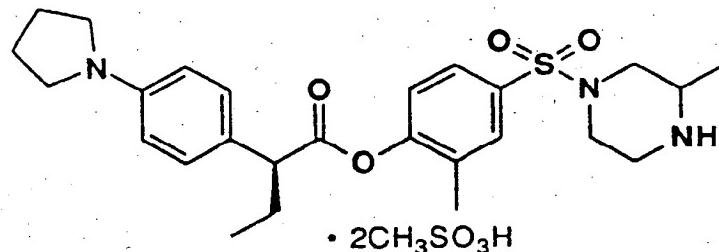


30 NMR (DMSO-d₆): δ 7.78 (1H, s), 7.67 (1H, dd, J=2 and 8Hz), 7.35-6.94 (7H, m), 6.80-6.64 (2H, br), 5.00-4.93

35 (1H, m), 3.70 (1H, t, J=7Hz), 3.39-2.96 (6H, m), 2.17-1.64 (2H, m), 2.04-1.94 (4H, m), 1.91 (3H, s), 0.87 (3H, t, J=7Hz);
TLC : Rf 0.30 (chloroform:methanol:water=4:1:0.1).

Example 2(282)

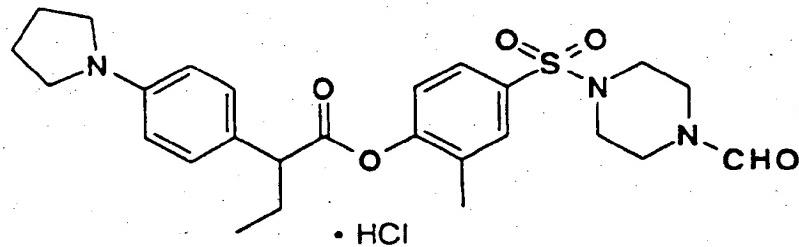
40 4-((2RS-methylpiperazin-4-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester
2methanesulfonic acid salt



Example 2(283)

20

4-((4-formylpiperazin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



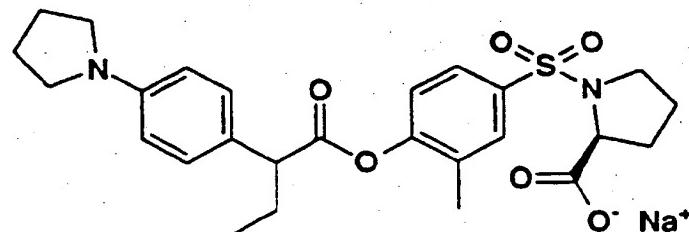
35

NMR (CD_3OD): δ 7.96 (1H, s), 7.73-7.52 (6H, m), 7.19 (1H, d, $J=8.4\text{Hz}$), 3.97 (1H, t, $J=7.6\text{Hz}$), 3.88-3.67 (4H, m), 3.67-3.44 (4H, m), 3.12-2.93 (4H, m), 2.43-2.14 (5H, m), 2.12-1.81 (4H, m), 1.00 (3H, t, $J=7.2\text{Hz}$);
TLC : Rf 0.38 (hexane:ethyl acetate=1:2).

Example 2(284)

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4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · sodium salt



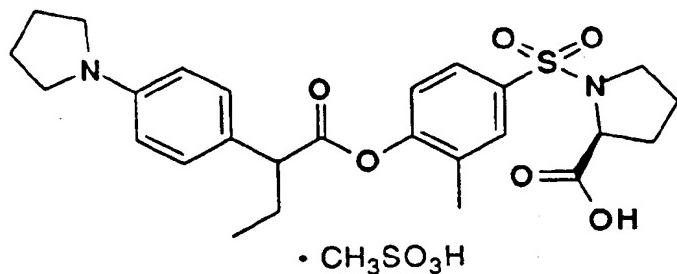
55

NMR ($d_6\text{-DMSO}$): δ 7.78-7.64 (2H, m), 7.18 (2H, d, $J=8.0\text{Hz}$), 7.08 (1H, d, $J=8.0\text{Hz}$), 6.53 (2H, d, $J=8.0\text{Hz}$), 3.95-3.80 (1H, m), 3.69 (1H, t, $J=7.5\text{Hz}$), 3.50-3.00 (6H, m), 2.20-1.30 (10H, m), 1.96 (3H, s), 0.91 (3H, t, $J=7.5\text{Hz}$);
TLC : Rf 0.32 (chloroform:methanol:water=9:1:0.1).

Example 2(285)

4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · methanesulfonic acid salt

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NMR (CDCl_3): δ 7.65 (4H, d, $J=8.5\text{Hz}$), 7.54 (2H, d, $J=8.5\text{Hz}$), 7.05 (1H, d, $J=8.5\text{Hz}$), 4.30-4.15 (1H, m), 4.10-3.50

(4H, m), 3.80 (1H, t, $J=7.5\text{Hz}$), 3.55-3.35 (1H, m), 3.30-3.10 (1H, m), 2.87 (3H, s), 2.50-1.60 (10H, m), 2.03 (3H, s), 0.99 (3H, t, $J=7.5\text{Hz}$);

TLC : R_f 0.32 (chloroform:methanol:water=9:1:0.1).

25

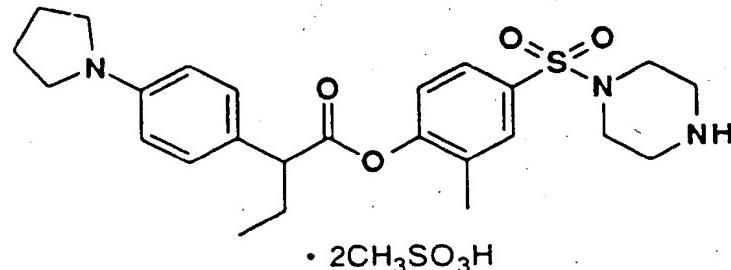
Example 2(286)

4-((piperazin-4-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2methanesulfonic acid salt

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NMR (CD_3OD): δ 7.75-7.60 (6H, m), 7.23 (1H, d, $J=8.0\text{Hz}$), 4.01 (1H, t, $J=7.5\text{Hz}$), 3.90-3.70 (4H, m), 3.35-3.20 (8H, m), 2.68 (6H, s), 2.40-1.80 (6H, m), 2.06 (3H, s), 1.00 (3H, t, $J=7.5\text{Hz}$);

TLC : R_f 0.14 (chloroform:methanol:acetic acid=40:2:1).

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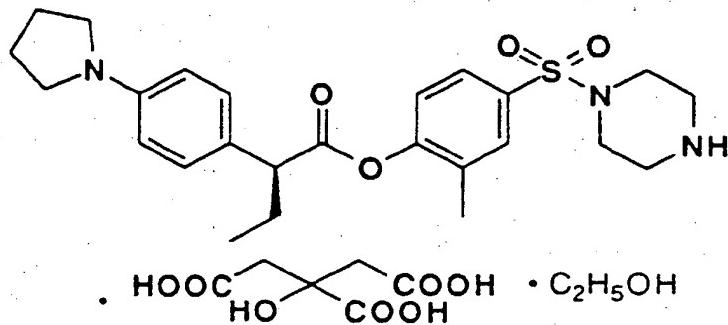
Example 2(287)

4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl) butanoic acid ester · citric acid salt · ethanol salt

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NMR (CD₃OD): δ 7.66 (1H, brs), 7.62 (1H, brd, J=8.0Hz), 7.20 (2H, d, J=8.5Hz), 7.18 (1H, d, J=8.0Hz), 6.58 (2H, d, J=8.5Hz), 3.67 (1H, t, J=7.5Hz), 3.60 (2H, q, J=7.0Hz), 3.40-3.15 (12H, m), 2.76 (4H, dd, J=8.0, 14.0Hz), 2.30-1.70 (9H, m), 1.17 (3H, t, J=7.0Hz), 0.97 (3H, t, J=7.5Hz);
TLC : R_f 0.11 (chloroform:methanol:acetic acid=40:2:1).

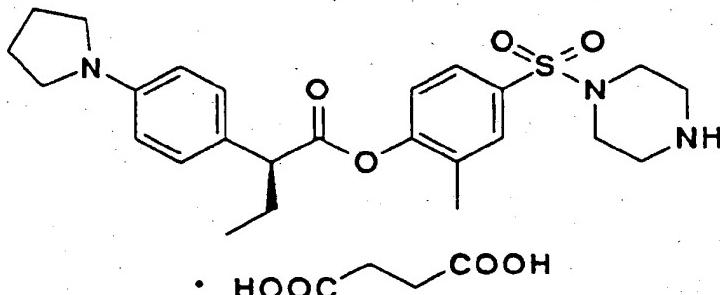
20 Example 2(288)

4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl)butanoic acid ester · succinic acid salt

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NMR (CD₃OD): δ 7.64 (1H, brs), 7.61 (1H, brd, J=8.0Hz), 7.19 (2H, d, J=8.5Hz), 7.17 (1H, d, J=8.0Hz), 6.57 (2H, d, J=8.5Hz), 3.64 (1H, t, J=7.5Hz), 3.40-3.20 (4H, m), 3.12 (8H, s), 2.51 (4H, s), 2.30-1.76 (9H, m), 0.97 (3H, t, J=7.5Hz);
TLC : R_f 0.11 (chloroform:methanol:acetic acid=40:2:1).

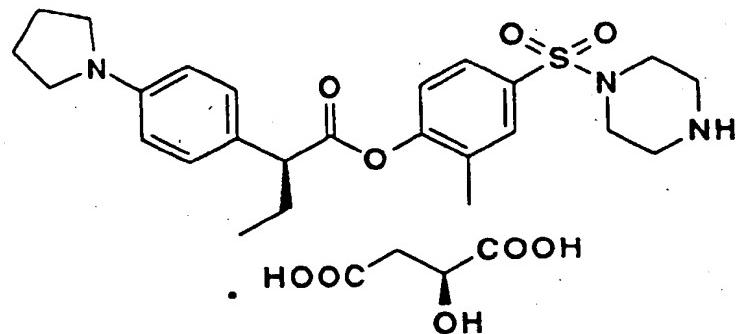
Example 2(289)

4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl)butanoic acid ester · L-malic acid salt

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NMR (CD_3OD): δ 7.67 (1H, brs), 7.62 (1H, brd, $J=8.0\text{Hz}$), 7.22 (2H, d, $J=8.5\text{Hz}$), 7.19 (1H, d, $J=8.0\text{Hz}$), 6.58 (2H, d, $J=8.5\text{Hz}$), 4.28 (1H, dd, $J=5.0, 7.5\text{Hz}$), 3.68 (1H, t, $J=7.5\text{Hz}$), 3.40-3.05 (12H, m), 2.78 (1H, dd, $J=5.0, 15.0\text{Hz}$), 2.52 (1H, dd, $J=7.5, 15.0\text{Hz}$), 2.40-1.72 (9H, m), 0.98 (3H, t, $J=7.5\text{Hz}$);

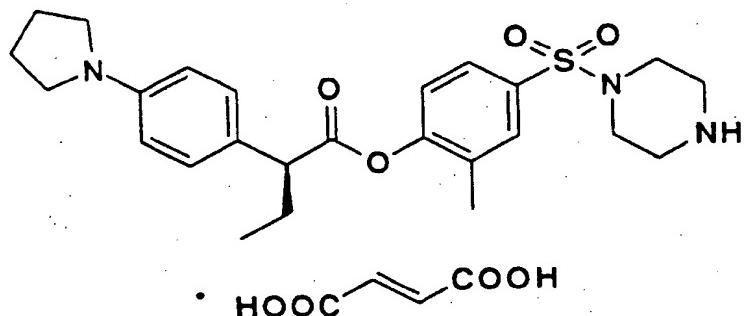
TLC : Rf 0.11 (chloroform:methanol:acetic acid=40:2:1).

20

Example 2(290)

4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl)butanoic acid ester · fumaric acid salt

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NMR (CD_3OD): δ 7.68 (1H, brs), 7.63 (1H, brd, $J=8.0\text{Hz}$), 7.21 (2H, d, $J=8.5\text{Hz}$), 7.19 (1H, d, $J=8.0\text{Hz}$), 6.82 (2H, s), 6.59 (2H, d, $J=8.5\text{Hz}$), 3.65 (1H, t, $J=7.5\text{Hz}$), 3.40-3.10 (12H, m), 2.30-1.70 (9H, m), 0.98 (3H, t, $J=7.5\text{Hz}$);

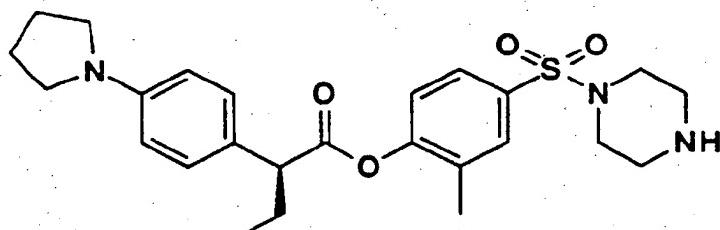
TLC : Rf 0.11 (chloroform:methanol:acetic acid=40:2:1).

Example 2(291)

45 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl)butanoic acid ester · oxalic acid salt

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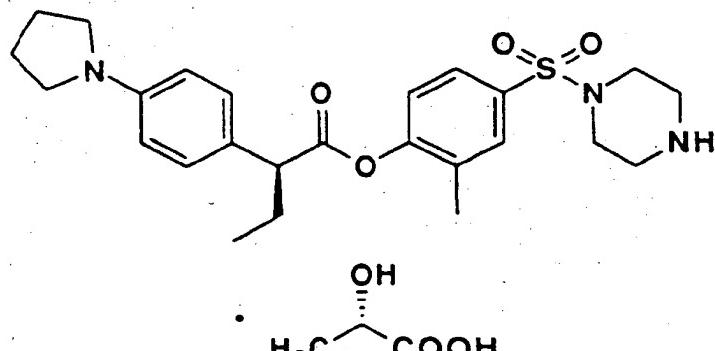
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15 NMR (CD₃OD): δ 7.68 (1H, s), 7.63 (1H, brd, J=8.0Hz), 7.20 (2H, d, J=8.5Hz), 7.19 (1H, d, J=8.0Hz), 6.60 (2H, d, J=8.5Hz), 3.66 (1H, t, J=7.5Hz), 3.45-3.10 (12H, m), 2.30-1.75 (9H, m), 0.98 (3H, t, J=7.5Hz);
TLC : R_f 0.11 (chloroform:methanol:acetic acid=40:2:1).

20 Example 2(292)

4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl)butanoic acid ester · L-lactic acid salt



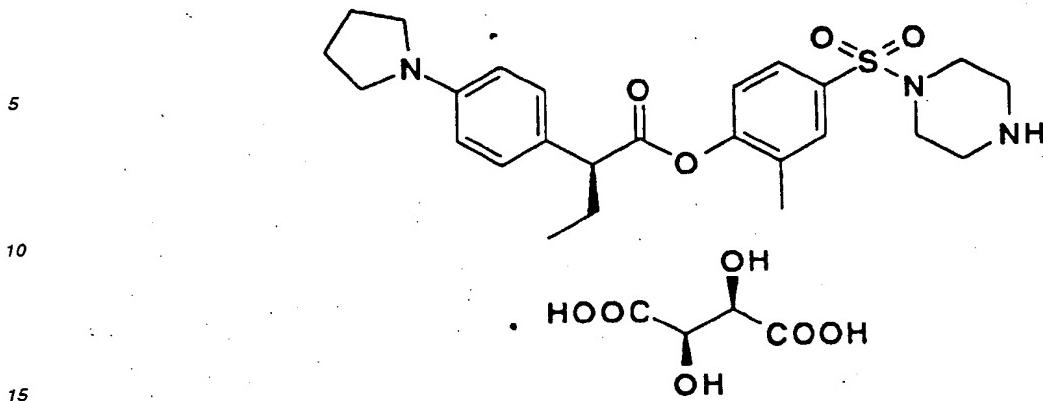
40 NMR (CD₃OD): δ 7.65 (1H, s), 7.61 (1H, brd, J=8.0Hz), 7.20 (2H, d, J=8.5Hz), 7.17 (1H, d, J=8.0Hz), 6.57 (2H, m, J=8.5Hz), 4.04 (1H, q, J=7.0Hz), 3.65 (1H, t, J=7.5Hz), 3.40-3.20 (4H, m), 3.14 (8H, s), 2.15 (3H, s), 2.20-1.75 (6H, m), 1.31 (3H, d, J=7.0Hz), 0.97 (3H, t, J=7.5Hz);
TLC : R_f 0.11 (chloroform:methanol:acetic acid=40:2:1).

45 Example 2(293)

4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl)butanoic acid ester · L-tartaric acid salt

50

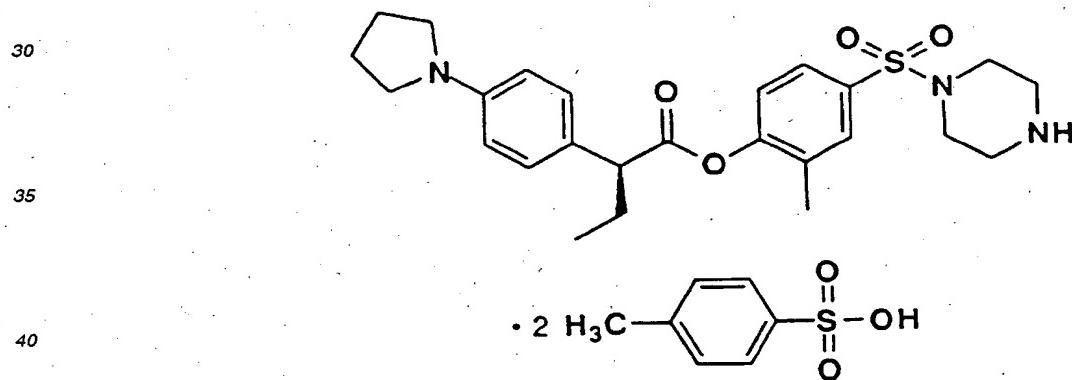
55



²⁰ NMR (CD_3OD): δ 7.68 (1H, s), 7.64 (1H, brd, $J=8.0\text{Hz}$), 7.21 (2H, d, $J=8.5\text{Hz}$), 7.18 (1H, d, $J=8.0\text{Hz}$); 6.59 (2H, d, $J=8.5\text{Hz}$), 4.43 (2H, s), 3.68 (1H, t, $J=7.5\text{Hz}$), 3.45 - 3.10 (12H, m), 2.40 - 1.78 (9H, m), 0.98 (3H, t, $J=7.5\text{Hz}$); TLC : Rf 0.11 (chloroform:methanol:acetic acid=40:2:1).

Example 2(294)

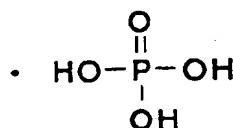
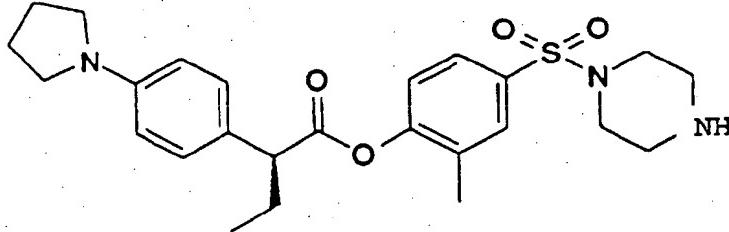
4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl)butanoic acid ester · 2 p-toluenesulfonic acid salt



45 NMR (CD_3OD): δ 7.68 (6H, d, $J=8.0\text{Hz}$), 7.63 (4H, d, $J=9.0\text{Hz}$), 7.22 (5H, d, $J=8.0\text{Hz}$), 3.99 (1H, t, $J=7.4\text{Hz}$), 3.83 - 3.65 (4H, m), 3.30 (8H, m), 2.36 (6H, s), 2.36-2.20 (5H, m), 2.04 (3H, s), 1.95 (1H, m), 0.99 (3H, t, $J=7.4\text{Hz}$);
TLC : Rf 0.11 (chloroform:methanol:acetic acid=40:2:1).

Example 2(295)

50 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl)butanoic acid ester - phosphoric acid salt

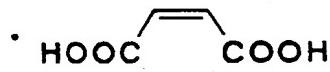
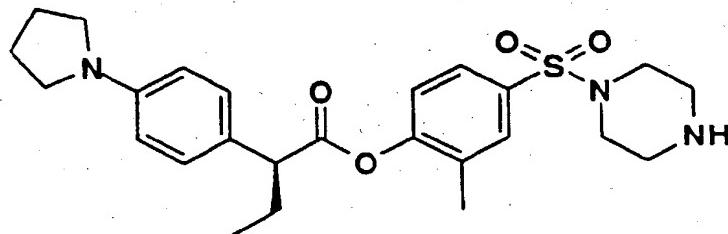


NMR (DMSO-d₆): δ 8.00-7.40 (3H, m), 7.67 (1H, brs), 7.62 (1H, brd, J=8.8Hz), 7.25 (1H, d, J=8.8Hz), 7.21 (2H, d, J=8.8Hz), 6.56 (2H, d, J=8.8Hz), 3.75 (1H, t, J=7.4Hz), 3.23 (4H, brs), 2.94 (8H, brs), 2.01 (3H, s), 2.20-1.80 (6H, m), 0.93 (3H, t, J=7.4Hz);

TLC : Rf 0.11 (chloroform:methanol:acetic acid=40:2:1).

Example 2(296)

25 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl)butanoic acid ester · maleic acid salt



40 NMR (CD₃OD): δ 7.67 (1H, s), 7.62 (1H, brd, J=8.0Hz), 7.20 (2H, d, J=8.5Hz), 7.19 (1H, d, J=8.0Hz), 6.58 (2H, d, J=8.5Hz), 6.23 (2H, s), 3.65 (1H, t, J=7.5Hz), 3.40-3.05 (12H, m), 2.30-1.78 (6H, m), 1.98 (3H, s), 0.97 (3H, t, J=7.5Hz);

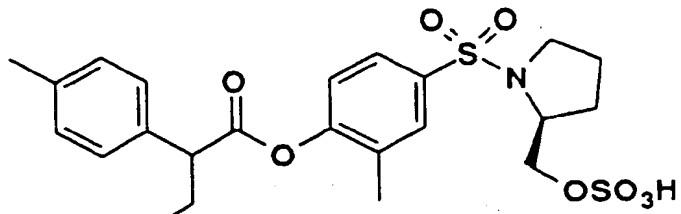
TLC : Rf 0.11 (chloroform:methanol:acetic acid=40:2:1).

45 Example 3

4-(2S-hydroxysulfonyloxy)methylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester

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To a solution of the compound prepared in example 2(19) (690 mg) in pyridine (10 ml) was added sulfur trioxide pyridine complex (766 mg) and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was concentrated, and the residue was purified by column chromatography on silica gel (chloroform:methanol=10:1) to give the title compound (700 mg) having the following physical data.

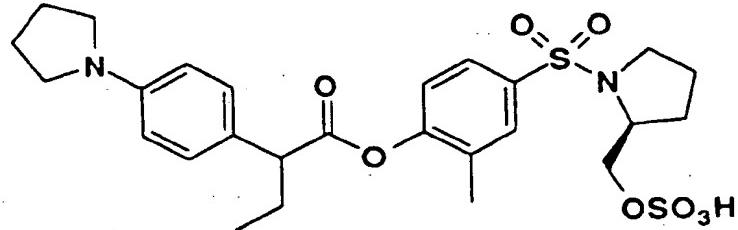
15 NMR (DMSO-d₆): δ 7.74 (1H, d, J=2.0Hz), 7.67 (1H, dd, J=8.5, 2.0Hz), 7.30 (2H, d, J=8.5Hz), 7.20 (2H, d, J=8.5Hz), 7.18 (1H, d, J=8.5Hz), 3.94-3.78 (2H, m), 3.76-3.60 (1H, m), 3.58 (1H, t, J=7.0Hz), 3.3-3.2 (1H, m), 3.12-2.94 (1H, m), 2.31 (3H, s), 2.25-2.00 and 1.95-1.70 (each 1H, m), 1.97 (3H, s), 1.90-1.60 (2H, m), 1.60-1.30 (2H, m), 0.91 (3H, t, J=7.5Hz);

20 TLC : Rf 0.39 (water:methanol:chloroform=1:10:40).

Example 3(1)

25 4-(2S-hydroxysulfonyloxyethyl)pyrrolidin-1-ylsulfonyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

30



35

40 By the same procedure as example 3, the title compound having the following physical data was given by using the compound prepared in example 2(10).

NMR (DMSO-d₆): δ 7.74 (1H, s), 7.67 (1H, d, J=8.5Hz), 7.25-7.10 (3H, m), 6.55 (2H, d, J=8.0Hz), 3.91 (1H, d, J=8.5Hz), 3.80-3.50 (3H, m), 3.40-3.20 (1H, m), 3.35-3.20 (4H, m), 3.15-2.90 (1H, m), 2.20-1.60 (2H, m), 1.98 (3H, s), 2.05-1.90 (4H, m), 1.90-1.60 (2H, m), 1.60-1.30 (2H, m), 0.91 (3H, t, J=7.5Hz);

TLC:Rf 0.38 (water:methanol:chloroform=1:10:40).

45

Formulation Examples

Formulation Example 1

50 The following components were admixed in conventional manner and punched out to obtain 100 tablets each containing 50 mg of active ingredient.

4-(piperazin-4-yl sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester 2 hydrochloride	5.0g
Carboxymethylcellulose calcium (disintegrating agent)	0.2g
Magnesium stearate (lubricating agent)	0.1g
Microcrystalline cellulose	4.7g

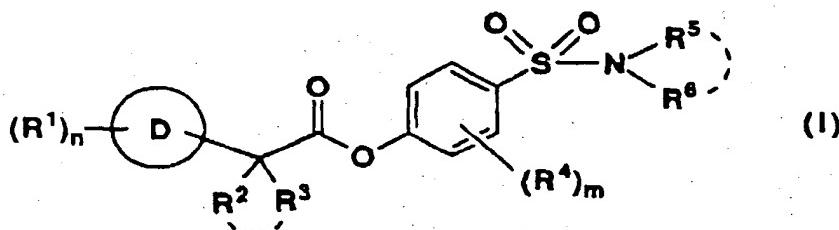
Formulation Example 2

The following components were admixed in conventional manner. The solution was sterilized in conventional manner, placed 5 ml portion into ampoules and freeze-dried to obtain 100 ampoules each containing 20 mg of the active ingredient.

4-(piperazin-4-yl sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester 2 hydrochloride	2.0g
mannitol	20 g
Distilled water	1000ml

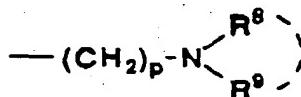
Claims

15 1. A sulfonamide derivative of the formula (I)



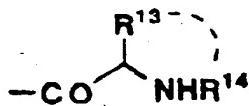
wherein R¹ is C1-8 alkyl, C1-8 alkoxy, hydroxy, keto, nitro, halogen atom, trihalomethyl, cyano, amidino, -COOR⁷ (in which R⁷ is hydrogen atom or C1-8 alkyl), or

30



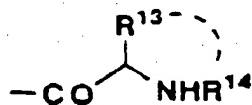
(in which p is an integer from 0 to 4, and R⁸ and R⁹ each, independently, is hydrogen atom, C1-4 alkyl, C2-5 acyl, -COOR¹⁰ (in which R¹⁰ is hydrogen atom or C1-8 alkyl), -CONR¹¹R¹² (in which R¹¹ and R¹² each, independently, is hydrogen atom or C1-4 alkyl),

40



(in which

50



55

Is an α-amino acid residue), or R⁸ and R⁹ taken together with the nitrogen atom to which they are attached represent an aliphatic heterocyclic

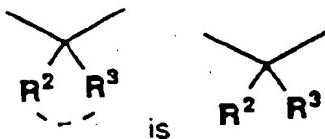
ring which is unsubstituted or substituted by C1-4 alkyl or phenyl C1-4 alkyl);
n is an integer from 0 to 5;

5



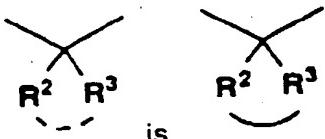
10 is a carbocyclic ring or heterocyclic ring;

15



20 in which R² and R³ each, independently, is hydrogen atom, C1-4 alkyl, C1-4 alkoxy, halogen atom, trihalomethyl or phenyl, or
R² and R³, taken together, represent C1-4 alkylidene, or

25



30 in which R² and R³, taken together with the carbon atom to which they are attached represent C3-7 cycloalkyl; R⁴ is C1-4 alkyl or C1-4 alkoxy or two of R⁴, attached to the benzene nucleus at ortho positions relative to each other, taken together, represent C3-5 alkylene;
m is an integer from 0 to 4; and

35



40

in which R⁵ and R⁶ each, independently, is

1) hydrogen atom,

2) hydroxy,

45

3) C1-8 alkyl,

4) C1-8 alkoxy

5) phenyl C1-4 alkoxy,

6) amidino,

7) -M-R¹⁶

50

(in which M is single bond or C1-8 alkylene), and

R¹⁶ is

i) -NR¹⁷R¹⁸ (in which R¹⁷ and R¹⁸ each, independently, is hydrogen atom or C1-4 alkyl),

ii) -CONR¹⁹R²⁰ (in which R¹⁹ and R²⁰ each, independently, is hydrogen atom or C1-4 alkyl),

iii)

55



5

(in which

10



15

is a carbocyclic ring,

r is an integer from 0 to 5, and

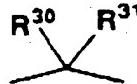
20 R²¹ is C1-4 alkyl, C1-4 alkoxy, nitro, amidino, -COOR²² (in which R²² is hydrogen atom, C1-8 alkyl, phenyl or phenyl C1-4 alkyl), -SO₃H, -CONR²³-E-R²⁴ (in which R²³ is hydrogen atom or C1-4 alkyl, E is 1-4 alkylene and R²⁴ is -COOR²⁵ (in which R²⁵ is hydrogen atom, C1-8 alkyl, phenyl or phenyl C1-4 alkyl) or tetrazole ring), tetrazole ring or morpholino ring),

iv) heterocyclic ring, unsubstituted or substituted by 1 to 4 substituents selected from C1-4 alkyl, C1-4 alkoxy, hydroxy, phenyl C1-4 alkyl, -COOR²⁶ (in which R²⁶ is hydrogen atom, C1-8 alkyl, phenyl or phenyl C1-4 alkyl), hydroxy C1-4 alkyl or C2-4 alkoxyalkyl),

25 8) C1-8 alkyl substituted by one or two of -OR²⁷ (in which R²⁷ is hydrogen atom, C1-4 alkyl, C2-4 alkoxyalkyl or C2-4 alkyl substituted by -OR²⁸ (in which R²⁸ is hydrogen atom or C2-4 alkoxyalkyl)),

9) -J-COOR²⁹ (in which R²⁹ is hydrogen atom, C1-8 alkyl, phenyl or phenyl C1-4 alkyl, and J is a single bond, -(CH₂)_s or

30



35

(in which s is an integer from 2 to 6, and

R<sup>30</sup> and R<sup>31</sup> each, independently, is

i) hydrogen atom,

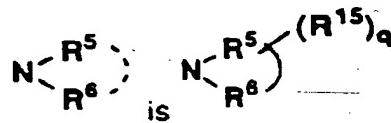
ii) C1-8 alkyl,

40 iii) -COOR³² (in which R³² is hydrogen atom, C1-8 alkyl, phenyl or phenyl C1-4 alkyl),

iv) carbocyclic or heterocyclic ring, unsubstituted or substituted by one or more substituents selected from C1-4 alkyl, C1-4 alkoxyalkyl, amino, nitro, hydroxy, halogen atom, nitrite, guanidino and amidino, or

v) C1-8 alkyl substituted by one or more substituents selected from hydroxy, -COOR³³ (in which R³³ is hydrogen atom, C1-8 alkyl, phenyl or phenyl C1-4 alkyl), -NR³⁴R³⁵ (in which R³⁴ and R³⁵ each, independently, is hydrogen atom or C1-4 alkyl), carbocyclic or heterocyclic ring, unsubstituted or substituted by one or more substituents selected from C1-4 alkyl, C1-4 alkoxyalkyl, amino, nitro, hydroxy, halogen atom, nitrile, guanidino and amidino, with the proviso that a carbon atom of C1-8 alkyl may be replaced by a sulfur atom), or

50



55

in which R⁵ and R⁶, taken together with the nitrogen atom to which they are attached represent a heterocyclic ring, q is an integer from 0 to 4, and

R<sup>15</sup> is

1) hydroxy,

- 2) keto,
 3) protected keto,
 4) C1-4 alkyl,
 5) C1-4 alkoxy,
 6) phenyl,
 7) phenoxy,
 8) phenyl C1-4 alkyl,
 9) phenyl C1-4 alkoxy,
 10) nitro,
- 11) -COOR³⁶ (in which R³⁶ is hydrogen atom, C1-8 alkyl, C1-4 alkyl substituted by -CONR³⁷R³⁸ (in which R³⁷ and R³⁸ each, independently, is hydrogen atom or C1-4 alkyl), C1-4 alkyl substituted by -NR³⁹R⁴⁰ (in which R³⁹ and R⁴⁰ each, independently, is hydrogen atom or C1-4 alkyl), C1-4 alkyl substituted by -OR⁴¹ (in which R⁴¹ is C2-4 alkyl substituted by -OR⁴² (in which R⁴² is hydrogen atom or C2-4 alkoxyalkyl)) or C1-4 alkyl substituted by piperazino ring),
- 12) -NR⁴³R⁴⁴ (in which R⁴³ and R⁴⁴ each, independently, is hydrogen atom, C1-4 alkyl or C2-5 acyl),
 13) -CONR⁴⁵R⁴⁶ (in which R⁴⁵ and R⁴⁶ each, independently, is hydrogen atom, hydroxy, C1-4 alkyl, phenyl C1-4 alkoxy or C1-4 alkyl substituted by hydroxy or -COOR⁴⁷ (in which R⁴⁷ is hydrogen atom or C1-8 alkyl)),
 14) C1-4 alkyl substituted by one or more substituents selected from hydroxy, -COOR⁴⁸ (in which R⁴⁸ is hydrogen atom or C1-8 alkyl), -NR⁴⁹R⁵⁰ (in which R⁴⁹ and R⁵⁰ each, independently, is hydrogen atom or C1-4 alkyl), -OSO₃H or 5- or 6-membered heterocyclic ring containing one or two nitrogen atoms,
 15) 5- or 6-membered heterocyclic ring containing one or two nitrogen atoms,
 16) halogen atom,
 17) -CHO, or
 18) -NR⁵¹-COOR⁵² (in which R⁵¹ and R⁵² each, independently, is hydrogen atom or C1-8 alkyl);
 or a non-toxic salt, acid addition salt or solvate thereof.

2. A compound according to claim 1, wherein



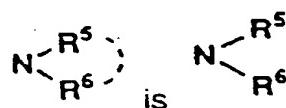
35 is 3-15 membered mono- or poly-cyclic aromatic hydrocarbon ring or aliphatic hydrocarbon ring.

3. A compound according to claim 1, wherein



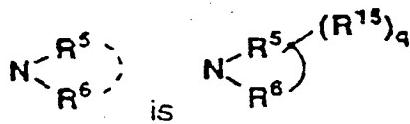
40 is 5-15 membered mono- or bi-cyclic aromatic heterocyclic ring, saturated heterocyclic ring or partly saturated heterocyclic ring containing one to four nitrogen atoms, one or two sulfur atoms, one or two oxygen atoms or one nitrogen atom and one sulfur atom or oxygen atom.

45 4. A compound according to any one of claims 1 to 3, wherein



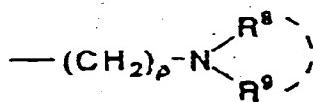
in which all symbols are as defined in claim 1.

5. A compound according to any one of claims 1 to 3, wherein



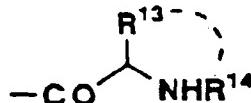
in which all symbols are as defined in claim 1.

15. 6. A compound according to any one of claims 1 to 5, wherein R¹ is C1-8 alkyl, C1-8 alkoxy, hydroxy, keto, nitro, halogen atom, trihalomethyl, cyano, amidino, -COOR⁷ (in which R⁷ is as defined in claim 1), or



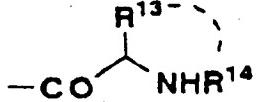
(in which p is as defined in claim 1, and

25 R⁸ and R⁹ each, independently, is hydrogen atom, C1-4 alkyl, C2-5 acyl, -COOR¹⁰ (in which R¹⁰ is as defined in claim 1), -CONR¹¹R¹² (in which R¹¹ and R¹² are as defined in claim 1),



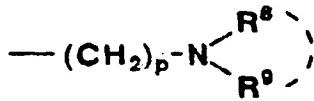
(in which

- 35 45. 7. A compound according to any one of claims 1 to 5, wherein R¹ is



is as defined in claim 1).

- 50
45. 7. A compound according to any one of claims 1 to 5, wherein R¹ is



in which R⁸ and R⁹ taken together with the nitrogen atom to which they are attached represent an aliphatic heterocyclic ring which is unsubstituted or substituted by C1-4 alkyl or phenyl C1-4 alkyl.

55. 8. A compound according to claim 1, which is

4-(2S-t-butyloxycarbonylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid

- ester,
 4-(2S-hydroxymethylpyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2-oxopyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(pyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 5 4-(2S-(pyrrolidin-1-ylmethyl)pyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(pyrrolidin-1-ylsulfonyl)phenyl 2RS-phenylbutanoic acid ester,
 4-(indolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 10 4-(2-(ethoxycarbonyl)indolin-1-ylsulfonyl)2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2-(ethoxycarbonyl)indolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2RS-(N,N-dimethylaminocarbonylmethoxycarbonyl)indolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 15 4-(2RS-(N-benzyloxycarbamoyl)indolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(6-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(6-aminoindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(7-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 20 4-(7-aminoindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(benzimidazol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(morpholin-4-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(6-aza-7-oxo-bicyclo[3.2.1]octan-6-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 25 4-(4-benzylpiperazin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(4-(2-hydroxyethyl)piperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2RS-hydroxymethylpiperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 30 25 4-(4-(N,N-dimethylamino)piperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(4-(pyrimidin-2-yl)piperazin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(1,4-dioxa-8-azaspiro[4.5]decan-8-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(3-azabicyclo[3.2.2]nonan-3-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(1,3,3-trimethyl-6-azabicyclo[3.2.1]octan-6-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid
 35 30 ester,
 4-(2-oxopiperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2-oxo-4S-benzyltetrahydroxazol-3-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2-oxo-4S-isopropylperhydroxazol-3-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2-oxo-4S-methyl-5S-phenylperhydroxazol-3-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid
 40 35 ester,
 4-(1RS-oxo-4S-methoxycarbonylperhydrothiazol-3-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(morpholin-4-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(imidazol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 40 45 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(morpholin-4-ylsulfonyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester,
 4-(morpholin-4-ylsulfonyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 4-(6-aza-7-oxobicyclo[3.2.1]octan-6-ylsulfonyl)phenyl 2RS-(4-methoxyphenyl)-2-ethylbutanoic acid ester,
 4-(morpholin-4-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester,
 45 50 4-(imidazol-1-ylsulfonyl)phenyl 2RS-phenylbutanoic acid ester,
 4-(morpholin-4-ylsulfonyl)phenyl 2RS-phenylbutanoic acid ester,
 4-(N-1RS-(ethoxycarbonyl)-2-(morpholin-4-yl)ethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-1RS-(ethoxycarbonyl)-2-(morpholin-4-yl)ethylsulfamoyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester,
 50 55 4-(N-1RS-(ethoxycarbonyl)-2-(morpholin-4-yl)ethylsulfamoyl)phenyl 2RS-phenyl-2-methoxyacetic acid ester,
 4-(N-benzyloxycarbonylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-1RS-phenyl-2RS-methylbutylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-sulfamoylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-2-methoxyethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-2-methoxyethyl-N-benzylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-t-butyloxysulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,

- 4-(N-4-hydroxybutylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-1RS-hydroxymethyl-2-methylpropylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-2RS,3-dihydroxypropylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-benzyloxysulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 5 4-(N-(N',N'-dimethylamino)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(N'-methylamino)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(carbamoylmethyl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-t-butylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-adamantan-1-ylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 10 4-guanidinosulfonyl-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-2RS,3-dihydroxypropylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N,N-bis(2-(methoxymethoxy)ethyl)sulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 15 4-(N,N-bis(2-(2-(methoxymethoxy)ethoxy)ethyl)sulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-methyl-N-methoxysulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-benzylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-2-(N',N'-dimethylamino)ethylsulfamoyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester,
 20 4-guanidinosulfonylphenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 4-guanidinosulfonylphenyl 2RS-(4-nitrophenyl)butanoic acid ester,
 4-(N-2RS,3-dihydroxypropylsulfamoyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester,
 4-(N-2-methoxyethylsulfamoyl)phenyl 2-(4-methoxyphenyl)-2-ethylbutanoic acid ester,
 4-(N-2-(N',N'-dimethylamino)ethylsulfamoyl)phenyl 2-(4-methoxyphenyl)-2-ethylbutanoic acid ester,
 4-(guanidinosulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester,
 25 4-(N,N-diethylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester,
 4-(N-benzylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester,
 4-(N-methyl-N-benzylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester,
 4-(N-2-phenylethylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester,
 4-(N-methyl-N-2-phenylethylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester,
 30 4-(N-1RS-(4-methylphenyl)butylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester,
 4-(N-2-(pyridin-2-yl)ethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-2-(piperidin-1-yl)ethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(tetrazol-5-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 35 4-(N-(morpholin-4-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(pyrrolidin-3-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(1-benzyl(piperidin-4-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(pyridin-2-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-2-(morpholin-4-yl)ethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(pyrazin-2-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 40 4-(N-(imidazol-2-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(quinuclidin-3RS-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(2,2,6,6-tetramethylpiperidin-4-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(quinuclidin-3RS-yl)sulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 45 4-(N-2-(morpholin-4-yl)ethylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-2-(piperazin-4-yl)ethylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(piperidin-4-yl)sulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-2-(morpholin-4-yl)ethylsulfamoyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester,
 4-(N-2-(pyridin-2-yl)ethylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 50 4-(N-2-(piperidin-1-yl)ethylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 4-(N-2-(1-methylpyrrol-2-yl)ethylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 4-(N-(tetrazol-5-yl)methyl)sulfamoyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester,
 4-(N-(tetrazol-5-yl)sulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 55 4-(N-(tetrazol-5-yl)sulfamoyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester,
 4-(N-(quinuclidin-3RS-yl)sulfamoyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester,
 4-(N-2R-methoxy-3R-hydroxy-4S-hydroxy-5R-hydroxyperhydropyran-6R-ylmethylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-phenylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester,

4-(N-4-nitrophenylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester,
 4-(N-phenylsulfamoyl)phenyl 2RS-(4-aminophenyl)butanoic acid ester,
 4-(N-(2-(tetrazol-5-yl)phenyl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-4-(morpholin-4-yl)phenylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 5 2-(N-(4-(2RS-(4-(pyrrolidin-1-yl)phenyl)butyloxy)-3-methylphenylsulfonyl)amino)phenylsulfonic acid
 4-(N-3,5-dimethoxyphenylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-phenylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 10 4-(N-2-(N'-(tetrazol-5-ylmethyl)carbamoyl)benzen-1-ylsulfamoyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester,
 4-(N-2-(N'-(tetrazol-5-ylmethyl)carbamoyl)benzen-1-ylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 4-(N-(4-amidinophenyl)sulfamoyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester,
 15 4-(N-(4-amidinophenyl)sulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 4-(N-2-(tetrazol-5-yl)phenylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 4-(N-4-(morpholin-4-yl)phenylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 20 4-(N-2-(tetrazol-5-yl)phenylsulfamoyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(N-t-butylloxycarbonylamino)phenyl)butanoic acid ester,
 4-(3,5-dimethoxybenzylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 25 4-((4-t-butoxycarbonylamino)perhydroxazol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-methoxy-N-benzylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-benzyloxy-N-methylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 30 4-(2-(N,N-dimethylamino)ethylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2-(piperidin-1-yl)ethylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(3-(morpholin-4-yl)propylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(indolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 35 4-((2-oxo-4R-isopropylperhydroxazol-3-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-2-(morpholin-4-yl)ethyl-N-methoxyaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(5-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 40 4-(morpholin-4-ylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(6-fluoroindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(5-(N,N-dimethylamino)indolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 45 4-(4-methylpiperazin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(5-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2-(morpholin-4-yl)ethylaminosulfonyl)-2-ethylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2-(morpholin-4-yl)ethylaminosulfonyl)-2-ethylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2-(morpholin-4-yl)ethylaminosulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 50 4-(2-(morpholin-4-yl)ethylaminosulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(4-methyl-1,4-perhydrodiazepin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2RS-ethoxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(quinuclidin-3RS-ylaminosulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2-(morpholin-4-yl)ethylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 55 4-(3,5-dimethoxyphenylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2S-carboxypyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2S-carboxypyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2R-carboxypyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2S-carboxy-4R-hydroxypyrrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2S-carboxy-4R-benzylloxypyrrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2S-carboxy-4S-aminopyrrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2S-carboxy-4R-aminopyrrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2S-(N-carboxymethylcarbamoyl)pyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,

4-(2S-(2-aminoethoxycarbonyl)pyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2S-(2-(2-hydroxyethoxy)ethoxycarbonyl)pyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 5 4-(2S-hydroxymethylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2S-(2-(piperazin-4-yl)ethyl)oxycarbonylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 10 4-(2S-carboxypyrrrolidin-1-ylsulfonyl)phenyl 2-(2-methoxyphenyl)-2-ethylbutanoic acid ester,
 4-(2S carboxypyrrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(2-methoxyphenyl)butanoic acid ester,
 4-(2S-carboxypyrrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester,
 4-(2S-(2-(piperazin-1-yl)ethyl)oxycarbonylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester,
 15 4-(2S-(2-(2-hydroxyethoxy)ethoxycarbonyl)pyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester,
 4-(2S-(2-aminoethyl)oxycarbonylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester,
 20 4-(2S-carboxypyrrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester,
 4-(2S-hydroxymethylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester,
 4-(2S-(2-aminoethyl)oxycarbonylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester,
 25 4-(2S-(2-(2-hydroxyethoxy)ethyl)oxycarbonylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester,
 4-(2S-carboxypyrrrolidin-1-ylsulfonyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester,
 4-(2S-carboxypyrrrolidin-1-ylsulfonyl)phenyl 2R-(4-nitrophenyl)butanoic acid ester,
 30 4-(2S-carboxypyrrrolidin-1-ylsulfonyl)phenyl 2S-(4-nitrophenyl)butanoic acid ester,
 4-(2S-carboxypyrrrolidin-1-ylsulfonyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 4-(2S-carboxypyrrrolidin-1-ylsulfonyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester,
 4-(2R-carboxypyrrrolidin-1-ylsulfonyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester,
 35 4-(2H-carboxypyrrrolidin-1-ylsulfonyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 4-(2S-carboxypyrrrolidin-1-ylsulfonyl)phenyl 2RS-phenylbutanoic acid ester,
 4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 40 4-(2S-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2S-carboxyperhydroindol-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2RS-carboxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2RS-(N-carboxymethylcarbamoyl)indolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 45 4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2RS-carboxy-3,3-dimethylindolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2RS-carboxyindolin-1-ylsulfonyl)-2-methoxyphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2RS-(N-2-carboxyethylcarbamoyl)indolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 50 4-(2RS-(N-2-hydroxyethylcarbamoyl)indolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2-carboxy-5,6-dimethoxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 55 4-(2RS-(2-aminoethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2-carboxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2RS-carboxy-5,6-dimethoxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2-carboxy-5-hydroxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2RS-(2-(2-hydroxyethoxy)ethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2RS-hydroxymethylindolin-1-ylsulfonyl)-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,

4-(2RS-carboxy-5-hydroxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2RS-(2-(piperazin-1-yl)ethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 5 4-(2RS-(N-hydroxycarbamoyl)indolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(4-methoxyphenyl)butanoic acid ester,
 4-(2RS-carboxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester,
 10 4-(2-carboxy-5,6-dimethoxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester,
 4-(2-carboxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester,
 4-(2-carboxy-5-hydroxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester,
 15 4-(2RS-hydroxymethylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester,
 4-(2RS-(2-aminoethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester,
 4-(2RS-(2-(piperazin-4-yl)ethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester,
 20 4-(2RS-(2-(2-hydroxyethoxy)ethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester,
 4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(3-methoxyphenyl)butanoic acid ester,
 4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(2-methoxyphenyl)butanoic acid ester,
 25 4-(2RS-carboxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(2-methoxyphenyl)butanoic acid ester,
 4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(3,4-dimethoxyphenyl)butanoic acid ester,
 4-(2RS-carboxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(3,4-dimethoxyphenyl)butanoic acid ester,
 4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(4-methylphenyl)butanoic acid ester,
 30 4-(2RS-carboxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester,
 4-(2-carboxy-5,6-dimethoxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester,
 4-(2-carboxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester,
 4-(2-carboxy-5-hydroxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester,
 35 4-(2RS-(2-aminoethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester,
 4-(2RS-hydroxymethylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester,
 4-(2RS-(2-(hydroxyethoxy)ethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester,
 4-(2RS-(2-(piperazin-4-yl)ethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester,
 40 35 4-(2RS-carboxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-hydroxyphenyl)butanoic acid ester,
 4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(4-aminophenyl)butanoic acid ester,
 4-(4S-carboxyperhydrothiazol-3-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(4-carboxypiperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2RS-carboxypiperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(3RS-carboxypiperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(4S-carboxyperhydrothiazol-3-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 45 4-(2RS-carboxymorpholin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(1S-oxo-4S-carboxyperhydrothiazol-3-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(4S-carboxy-1,1-dioxoperhydrothiazol-3-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(4-(2-hydroxyethyl)piperazin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 50 55 4-(4-carboxymethylpiperazin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(4S-carboxyperhydrothiazol-3-ylsulfonyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester,
 4-(N-carboxymethyl-N-2-methoxyethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-1RS,2-dicarboxyethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(1-carboxycyclobutane)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-1RS-carboxy-2-phenylethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-1S-carboxy-2-methylpropylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(1S-carboxy-2-carboxymethylthioethyl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,

- 4-(N-1RS-carboxy-1-(thiophen-2-yl)methylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-1RS-carboxy-1-(furan-2-yl)methylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-carboxymethyl-N-2-methoxyethylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-propyl-N-carboxymethylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-1S-carboxy-5-aminopentylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-carboxymethylsulfamoyl)phenyl 2-(4-methoxyphenyl)-2-ethylbutanoic acid ester,
 4-(N-2-methoxyethyl-N-carboxymethylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 4-(N-1RS,2-dicarboxyethylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 4-(N-carboxymethylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester,
 4-(N-propyl-N-carboxymethylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester,
 4-(N-benyl-N-carboxymethylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester,
 4-(N-2-phenylethyl-N-carboxymethylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester,
 4-(N-phenyl-N-carboxymethylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester,
 4-(N,N-bis(2-hydroxyethyl)sulfamoyl)-2-methyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N,N-bis(2-(2-hydroxyethoxy)ethyl)sulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(3RS-carboxy-1,4-benzodioxan-5-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-2RS-hydroxy-4R-hydroxy-5R-hydroxy-6R-hydroxymethylperhydropyran-3R-ylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-3-carboxyadamantan-1-ylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(1S,4R,3R-carboxybicyclo[2.2.1]heptan-2S-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-3S-carboxycyclohexane-1R-ylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-2RS-carboxycyclohexane-1RS-ylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(naphthalen-1-yl)acetic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(naphthalen-2-yl)acetic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(cyclohexane-1-yl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-phenylbutanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-phenyl-2-ethylbutanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-phenylpropanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2R-phenylbutanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2S-phenylbutanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-phenyl-2-methylpropanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-phenylcyclohexanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-phenylcyclopropanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-phenylcyclopantanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-phenylcyclobutanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-phenylacetic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-chloro-2-phenylacetic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-chloro-2-phenylbutanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2,2-diphenylbutanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-methyl-2-phenylbutanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2R-trifluoromethyl-2-phenyl-2-methoxyacetic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2S-trifluoromethyl-2-phenyl-2-methoxyacetic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-methoxyphenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-methoxyphenyl)-3-methylbutanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(4-methoxyphenyl)-2-methylpropanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-methoxyphenyl)propanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(4-methoxyphenyl)-2-ethylbutanoic acid ester.

- 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-methoxyphenyl)cyclohexanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-methoxyphenyl)cyclopentanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-methoxyphenyl)cyclobutanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-methoxyphenyl)cyclopropanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(3,4-dimethoxyphenyl)-2-ethylbutanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(3,4-dimethoxyphenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(3-methoxyphenyl)-2-ethylbutanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(2-methoxyphenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(2-methoxyphenyl)-2-ethylbutanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(3-methoxyphenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(2-methoxyphenyl)cyclobutanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2,6-dimethylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2-isopropylphenyl 2RS-(4-methoxyphenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(2-methylpropyloxy)phenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-isopropyoxyphenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-propyoxyphenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-methylphenyl)pentanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-methylphenyl)cyclopentanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(3-methylphenyl)cyclopentanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(2-methylphenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(2-methylphenyl)-2-ethylbutanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-methylphenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-nitrophenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(4-nitrophenyl)-2-methylpropanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclopropanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclopentanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(4-nitrophenyl)-2-ethylbutanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2-methylphenyl 2RS-(4-nitrophenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2-methylphenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2-methylphenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2,3-dimethylphenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester,
 7-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2,3-dihydroinden-4-yl 1-(4-nitrophenyl)cyclobutane-carboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,

- 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-3-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2,3-dimethylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 5 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-(pyrrolidin-1-yl)phenyl)cyclobutanecarboxylic acid ester,
 7-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2,3-dihydroinden-4-yl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 10 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2,6-dimethylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)-2-isopropylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 15 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(piperidin-1-yl)phenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(perhydroazepin-1-yl)phenyl)butanoic acid ester,
 20 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(aminophenyl)-2-ethylbutanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(aminophenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(N,N-dimethylamino)phenyl)butanoic acid ester,
 25 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-(N,N-dimethylamino)phenyl)cyclobutane-carboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(N,N-diethylaminomethyl)phenyl)butanoic acid ester,
 30 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-hydroxyphenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-cyanophenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-carboxyphenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-trifluoromethylphenyl)butanoic acid ester,
 35 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-amidinophenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(imidazolin-2-yl)phenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-chlorophenyl)cyclobutanecarboxylic acid ester,
 40 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(2-chlorophenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(2-chlorophenyl)-2-ethylbutanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(2-chlorophenyl)cyclobutanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-chlorophenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(3-nitro-4-hydroxyphenyl)butanoic acid ester,
 45 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(2-chloro-5-nitrophenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(2-chloro-5-nitrophenyl)cyclobutanecarboxylic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(3-nitro-4-chlorophenyl)cyclobutanecarboxylic acid ester,
 50 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(3-nitro-4-chlorophenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-ureidophenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-ureidophenyl)cyclobutanecarboxylic acid ester,
 55 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(N-(2S-aminopropionyl)amino)phenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(N-(2S-amino-3-methylbutyl)amino)
 phenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(N-(pyrrolidin-2S-ylcarbonyl)amino)
 phenyl)butanoic acid ester,

4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(3,4,5-trimethoxyphenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(2,4,6-trimethylphenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(3-nitro-4-methoxyphenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(3-nitro-4-aminophenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(N-acetylamino)phenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(N-methyl-N-acetylamino)phenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(morpholin-4-ylmethyl)phenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(4-benzylpiperazin-1-yl)phenyl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-ylmethyl)phenyl)butanoic acid ester,
 4-((1R-oxo-4S-carboxyperhydrothiazol-3-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2R-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2R-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S-aminomethylpyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((4-aminopiperdin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S-carboxyazetidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2RS-carboxypiperidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2-oxo-5S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(3-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S-carboxy-4R-methoxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2R-carboxy-4R-methoxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S-carboxy-4R-hydroxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-methoxy-N-carboxymethylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(2-methoxy-4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S-carboxyaziridin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N,N-bis(2-aminoethyl)aminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-carboxymethyl-N-(2-(N',N'-dimethylamino)ethyl)aminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-ethylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-carboxymethyl-N-bentyoxyaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(4-carboxybutyl)aminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(1,1-dimethyl-1-carboxymethyl)aminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-methyl-N-hydroxyaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(2-methyl-4-nitrophenyl)butanoic acid ester,
 4-(N-carboxymethylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-(1,1-dimethyl-1-carboxymethyl)-N-propylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,

4-((2S-carboxy-4S-aminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S-carboxy-4R-aminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 5 4-(N-carboxymethyl-N-(2-(morpholin-4-yl)ethyl)aminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S-carboxy-4S-acetylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 10 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)-2-butenoic acid ester,
 4-((2S-carboxy-4R-acetylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 15 4-((2RS-carboxy-5-nitroindolin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(2-methoxy-4-nitrophenyl)butanoic acid ester,
 4-((2S-carboxy-4S-methylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 20 4-((2S-carboxy-4S-(N,N-dimethylamino)pyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(N-hydroxyaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S,6S-dimethylpiperazin-4-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2RS-methylpiperazin-4-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S-carboxy-4R-(N,N-dimethylamino)pyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 25 4-((2S-carboxy-4R-methylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(piperazin-4-ylsulfonyl)-2-ethylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(piperazin-4-ylsulfonyl)-2-ethylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 30 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S-carboxymethylpyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2S-carboxy-4-acetylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 35 4-((2-carboxy-5,6-dimethoxyindol-1-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2RS-carboxyindolin-1-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((2RS-methylpiperazin-4-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-((4-formylpiperazin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 40 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 4-(2S-hydroxysulfonyloxymethylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester,
 4-((2S-hydroxysulfonyloxymethylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 45 or a non-toxic salt, acid addition salt or solvate thereof.

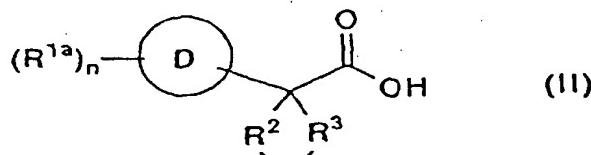
9. A compound according to claim 1, which is

50 4-(2S-carboxypyrrolidin-1-ylsulfonyl)phenyl 2RS-(2H-1,4-benzoxazin-3-on-6-yl)butanoic acid ester,
 4-(2R-carboxypyrrolidin-1-ylsulfonyl)phenyl 2RS-(2H-1,4-benzoxazin-3-on-6-yl)butanoic acid ester,
 4-(2S-carboxypyrrolidin-1-ylsulfonyl)phenyl 2RS-(2-methylbenzimidazol-5-yl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(1,3-benzodioxol-5-yl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(thiophen-2-yl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(1,3-benzodioxol-5-yl)-2-ethylbutanoic acid ester,
 55 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(thiophen-2-yl)-3-methylbutanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(pyridin-3-yl)butanoic acid ester,

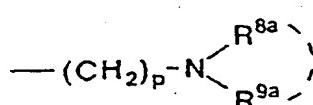
4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(2H-1,4-benzoxazin-3-on-6yl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(2-(N-methoxycarbonylamino)thiazol-4-yl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(2-methylbenzimidazol-5-yl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(1H-1-methyl-2-pyridon-3-yl)butanoic acid ester,
 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(thiophen-2-yl)-2-ethylbulanoic acid ester,

or a non-toxic salt, acid addition salt or solvate thereof.

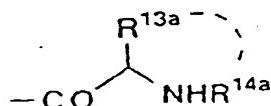
- 10 10. A pharmaceutical composition which comprises, as active ingredient, an effective amount of a compound of the formula (I) defined in claim 1, a non-toxic salt thereof, an acid addition salt thereof or a solvate thereof, with a carrier or coating.
- 15 11. A compound of the formula (I) or a non-toxic salt thereof or a non-toxic acid addition salt thereof or solvate thereof for use in the manufacture of pharmaceutical composition as an inhibitor of elastase.
- 20 12. A compound of the formula (I) or a non-toxic salt thereof or a non-toxic acid addition salt thereof or solvate thereof for use in the manufacture of a pharmaceutical composition for the prevention and/or the treatment of diseases induced by an abnormal enhancement of the degradation of elastin, collagen fiber and/or proteoglycan, resulting from the action of elastase on a mammalian animal, especially a human (e.g., chronic obstructive pulmonary disease such as emphysema, rheumatoid arthritis, atherosclerosis, adult respiratory distress syndrome (ARDS), glomerular nephritis, myocardial infarction, idiopathic ulcerative colitis or gingivitis).
- 25 13. A process for the preparation of a sulfonamide derivative of formula (I) as defined in claim 1 which process comprises esterifying a compound of the formula:



40 wherein R^{1a} is C1-8 alkyl, C1-8 alkoxy, hydroxy, protected hydroxy, keto, nitro, halogen atom, trihalomethyl, cyano, amidino, -COOR^{7a} (in which R^{7a} is C1-8 alkyl or benzyl), or

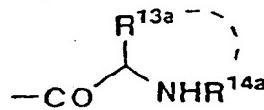


50 (in which p is as defined in claim 1, R^{8a} and R^{9a} each, independently, is hydrogen atom (with the proviso that, R^{8a} and R^{9a} do not represent hydrogen atom at the same time), t-butoxycarbonyl, benzyloxycarbonyl, C1-4 alkyl, C2-5 acyl, -COOR^{10a} (in which R^{10a} is C1-8 alkyl or benzyl), -CONR¹¹R¹² (in which R¹¹ and R¹² are as defined in claim 1), or



(in which

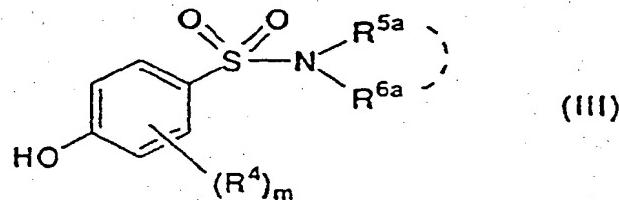
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- 10 is a protected α -amino acid residue), or
R^{8a} and R^{9a}, taken together with the nitrogen atom to which they are attached represent an aliphatic heterocyclic ring which is unsubstituted or substituted by C1-4 alkyl or phenyl C1-4 alkyl, and the other symbols are as defined in claim 1 with a compound of formula (III)

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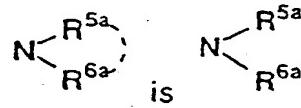
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wherein

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(in which R^{5a} and R^{6a} each, independently, is1) hydrogen atom (with the proviso that, R^{5a} and R^{6a} do not represent hydrogen atom at the same time),

2) hydroxy,

3) hydroxy protected by a protecting group which is removable under acid conditions,

4) t-butoxycarbonyl,

5) benzyloxycarbonyl,

6) C1-8 alkyl,

7) C1-8 alkoxy,

8) phenyl C1-4 alkoxy,

9) amidino,

10) -M-R^{16a} (in which M is as defined in claim 1, and R^{16a} is i) -NR^{17a}R^{18a} (in which R^{17a} and R^{18a} each, independently, is hydrogen atom (with the proviso that, R^{17a} and R^{18a} do not represent hydrogen atom at the same time), t-butoxycarbonyl, benzyloxycarbonyl or C1-4 alkyl), ii) -CONR^{19a}R^{20a} (in which R^{19a} and R^{20a} are as defined in claim 1),

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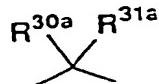


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55 (in which all the symbols are as hereinbefore defined), iv) heterocyclic ring, unsubstituted or substituted by 1 to 4 substituents selected from C1-4 alkyl, C1-4 alkoxy, hydroxy, phenyl C1-4 alkyl, -COOR²⁶ (in which R²⁶ is as defined in claim 1), hydroxy C1-4 alkyl in which hydroxy is protected by a protecting group which is removable under acid conditions or C2-4 alkoxyalkyl),

11) C1-8 alkyl substituted by one or two of -OR^{27a} (in which R^{27a} is hydrogen atom, C1-4 alkyl, C2-4 alkoxyalkyl, t-butyldimethylsilyl, THP, benzyl, or C2-4 alkyl substituted by -OR^{28a} (in which R^{28a} is hydrogen atom, C2-4 alkoxyalkyl, t-butyldimethylsilyl, THP or benzyl)).

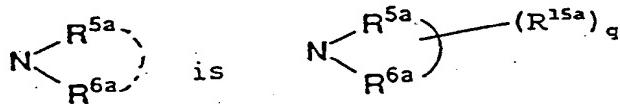
12) -Ja-COOR²⁹ (in which R²⁹ is as defined in claim 1 Ja is a single bond, -(CH₂)_s- or



10 (in which s is as defined in claim 1,

R^{30a} and R^{31a} each, independently, is i) hydrogen atom, ii) C1-8 alkyl, iii) -COOR³² (in which R³² is as defined in claim 1), iv) carbocyclic or heterocyclic ring, unsubstituted or substituted by one or more substituents selected from C1-4 alkyl, C1-4 alkoxyalkyl, amino, nitro, hydroxy, protected hydroxy, halogen atom, nitrile, guanidino and amidino, or v) C1-8 alkyl substituted by one or more substituents selected from hydroxy, protected hydroxy, -COOR³³ (in which R³³ is as defined in claim 1), -NR^{34a}R^{35a} (in which R^{34a} and R^{35a} each, independently, is hydrogen atom (with the proviso that, R^{34a} and R^{35a} do not represent hydrogen atom at the same time)), t-butoxycarbonyl, benzylloxycarbonyl or C1-4 alkyl), carbocyclic or, heterocyclic ring, unsubstituted or substituted by one or more substituents selected from C1-4 alkyl, C1-4 alkoxyalkyl, protected amino, nitro, hydroxy, protected hydroxy, halogen atom, nitrile, guanidino and amidino, with the proviso that a carbon atom of C1-8 alkyl may be replaced by a sulfur atoms, or

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in which R^{5a} and R^{6a}, taken together with the nitrogen atom to which they are attached represent a heterocyclic ring, q is as defined in claim 1.

30 R^{15a} is

- 1) hydroxy,
- 2) hydroxy protected by a protecting group which is removable under acid conditions,

35 3) keto,

4) protected keto,

5) C1-4 alkyl,

6) C1-4 alkoxy,

7) phenyl,

8) phenoxy,

9) phenyl C1-4 alkyl,

40 10) phenyl C1-4 alkoxy,

11) nitro,

45 12) -COOR^{36a} (in which R^{36a} is hydrogen atom, C1-8 alkyl, C1-4 alkyl substituted by -CONR³⁷R³⁸ (in which R³⁷ and R³⁸ are as defined in claim 1), C1-4 alkyl substituted by -NR^{39a}R^{40a} (in which R^{39a} and R^{40a} each, independently, is hydrogen atom (with the proviso that, R^{39a} and R^{40a} do not represent hydrogen atom at the same time)), t-butoxycarbonyl, benzylloxycarbonyl or C1-4 alkyl), C1-4 alkyl substituted by -OR^{41a} (in which R^{41a} is C2-4 alkyl substituted by -OR^{42a} (in which R^{42a} is hydrogen atom, C2-4 alkoxyalkyl or benzyl) or C1-4 alkyl substituted by protected piperazino ring),

50 13) -NR^{43a}R^{44a} (in which R^{43a} and R^{44a} each, independently, is hydrogen atom (with the proviso that, R^{43a} and R^{44a} do not represent hydrogen atom at the same time)), t-butoxycarbonyl, benzylloxycarbonyl, C1-4 alkyl or C2-5 acyl).

55 14) -CONR^{45a}R^{46a} (in which R^{45a} and R^{46a} each, independently, is hydrogen atom, C1-4 alkyl, hydroxy, hydroxy protected by a protecting group which is removable under acid conditions, phenyl C1-4 alkoxy or C1-4 alkyl substituted by hydroxy, protected hydroxy or -COOR^{47a} (in which R^{47a} is hydrogen atom, C1-8 alkyl or benzyl)),

15) C1-4 alkyl substituted by one or more substituents selected from hydroxy, protected hydroxy, -COOR^{46a} (in which R^{46a} is hydrogen atom, C1-8 alkyl or benzyl), -NR^{49a}R^{50a} (in which R^{49a} and R^{50a} each, independently, is hydrogen atom (with the proviso that, R^{49a} and R^{50a} do not represent hydrogen atom at the same time)), t-butoxycarbonyl, benzylloxycarbonyl or C1-4 alkyl), or 5- or 6-membered heterocyclic ring containing one or two nitrogen atoms,

EP 0 769 498 A1

- 16) 5- or 6-membered heterocyclic ring containing one or two nitrogen atoms,
17) halogen atom,
18) -CHO protected by a protecting group which is removable under acid conditions, or
19) -NR^{51a}-COOR^{52a} (in which R^{51a} and R^{52a} each, independently, is hydrogen atom or C1-8 alkyl), and the other symbols are as defined in claim 1, or
5 may be prepared by esterifying a compound of formula (II) with a compound of formula (III) to obtain a compound having protected group(s) and then eliminating the protecting groups,
or may be prepared by esterifying a compound of formula (II) with a compound of formula (III), if necessary, eliminating the protecting groups to obtain a compound having R¹⁵ represent C1-4 alkyl substituted by hydroxy, and
10 then subjecting to sulfuric acid esterification and optionally converting a compound of formula (I) thus obtained into a non-toxic salt, acid addition salt or solvate thereof.

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EUROPEAN SEARCH REPORT

Application Number

EP 96 30 7048

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y,D	EP 0 484 949 A (CORTECH INC) 13 May 1992 * the whole document *	1-13	C07D403/12 A61K31/635 A61K31/40 C07D207/06 C07C311/37 C07C311/44 C07D403/14 C07D413/12 C07D405/14 C07D417/12 C07D295/32 C07D207/28 C07D233/60 C07D401/12 C07D213/04 C07D207/32 C07D257/04 C07D211/10
Y,D	EP 0 465 802 A (CORTECH INC) 15 January 1992 * the whole document *	1-13	
Y	WO 93 11760 A (CORTECH INC) 24 June 1993 * the whole document *	1-13	
Y	EP 0 539 223 A (ONO PHARMACEUTICAL CO) 28 April 1993 * the whole document *	1-13	
Y,D	EP 0 347 168 A (ONO PHARMACEUTICAL CO) 20 December 1989 * the whole document *	1-13	
Y	EP 0 222 608 A (ONO PHARMACEUTICAL CO) 20 May 1987 * the whole document *	1-13	
Y	TRENDS IN PHARMACOLOGICAL SCIENCE, vol. 8, August 1987, AMSTERDAM, pages 303-307, XP002024127 TRAINOR,D.A. : "Synthetic inhibitors of human neutrophil elastase" * the whole document *	1-13	C07D
Y	ANNU.REP.MED.CHEM., vol. 29, 1994, NEW YORK, pages 195-204, XP000650529 HLASTA,D.J. ET AL.: "Human Leukocyte Elastase Inhibitors" * the whole document *	1-13	
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
MUNICH	29 January 1997	Stellmach, J	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			



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EUROPEAN SEARCH REPORT

Application Number

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
			C07D405/12 C07D207/16 C07D209/18 C07D409/12 C07D317/12 C07D333/24 C07D265/32 C07D213/64 C07D223/04 C07D233/06 //(C07D403/12, 207:00, 207:00), (C07D403/12, 209:00, 207:00), (C07D403/12, 233:00,
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
	The present search report has been drawn up for all claims		
Place of search	Date of completion of the search	Examiner	
MUNICH	29 January 1997	Stellmach, J	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone	T : theory or principle underlying the invention		
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Application Number
EP 96 30 7048

DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
		<p>207:00), (C07D403/12, 265:00, 207:00), (C07D403/12, 241:00, 207:00), (C07D403/12, 241:00, 207:00), (C07D403/12, 211:00,207:00)</p>
		<p>TECHNICAL FIELDS SEARCHED (Int.Cl.6)</p>
<p>The present search report has been drawn up for all claims</p>		
Place of search	Date of completion of the search	Examiner
MUNICH	29 January 1997	Stellmach, J
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p>		
<p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>		

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